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PLANNING CARE FOR THE GERIATRIC PATIENT*

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In recent years there has been quite general acceptance of the concept that care of the geriatric patient requires the multiple services of a wide variety of health, social and educational workers. Not only are the problems of the geriatric patient, whether they arise from his overt illness or from the need to promote and preserve his health, numerous, but frequently one problem actually reinforces another. For example, the patient who needs help in daily living activities may also need desperately to be assured that he is not being a burden to his family. Instructing his daughter, if she is already overburdened with care of a household and small children, to give him care, may keep him groomed, fed, and moved in and out of bed but it may also make him feel more useless and frustrated than ever, and hence may actually retard his rehabilitation. It may be wiser to have care given by the community nurse, or by a volunteer supervised by her. On the other hand, undiscriminating use of community facilities in providing care may reduce family cohesion and responsibility, and lead to the all-too-frequently observed picture of the long-term patient who is medically ready to go home from the hospital but whose family is not ready to resume caring for him. The nature and complexity of these problems make it evident that different kinds of skills are needed in geriatric care.

It is also quite generally accepted that these multiple professional services, often rendered by several different agencies or individuals, and the efforts of the patient and his family must represent a unified whole, with the services of all planned and carried out in consonance. Such a coordinated approach has come to be referred to as the "team" approach. This ordered use of many different services is needed just as much by the patient receiving care at home under the direction of the family physician as it is by the patient who secures care from one of the large medical centers or community agencies.

It is not the purpose of this paper to reiterate the need for team care of the geriatric patient, or the kinds of professional skills required in it, but rather to

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discuss some of the administrative and human relations problems that arise in making this concept work, and some of the practical measures that may be taken in planning for care of the geriatric patient.

THE MODEL FOR TEAM OPERATION

In establishing the model of how a team should work to provide care for the geriatric patient, it is necessary to consider two distinct qualities of the operation. The first is its *effectiveness*—the degree to which it accomplishes the job it sets out to do. The second aspect of importance, if we are to reach those who need help with the resources likely to be available, is that of *efficiency*—the degree to which the costs in terms of manpower, physical facilities and emotional stress are kept to the minimum consistent with the quality of work expected. These costs cannot be equated with dollar costs; for example, the most efficient use of short-supply manpower may cost more per unit of service, but may increase the quality to a desired level. However, efficient team operation should in many instances be reflected in substantial dollar savings per quality-unit of service produced. These two aspects must be kept in balance in the provision of service. A most *effective* service to patients with psychiatric problems may be rendered by a team of psychiatrist, psychologist, psychiatric social worker, psychiatric nurse and secretary in a clinic in which it is possible to provide for 4 or 5 patient consultations in a half day. However, it is obvious that only a fraction of the patients in the community who need such service could be reached by this method. The reconsideration of quality goals and the application of methods to promote efficiency may make it possible to care for more patients without sacrificing the effectiveness of the operation too greatly.

Agreement on the goals for care of the patient is of prime importance. All too often it seems that health agencies and practitioners are selling services rather than caring for people. Great care and thoughtfulness may be lavished on the provision of the technical services afforded by an outpatient department, with no consideration of the effect of the method of delivery of aid on the personality or emotional health of the individual. Think, for instance, of how often we place the clinic patient in the position of being always the recipient of service, never the contributor. It is interesting to speculate about what would happen to some of our "hard core" patients (in relation to their feeling of responsibility for their own care) if ways were found for them to contribute to the clinic or to help other patients.

The problems selected here as typical of those encountered in implementing a program for team care will be related to both effectiveness and efficiency.

It is necessary to differentiate between multi-professional care as such, and team care. In true team care, the services of the various professional and ancillary workers are planned and coordinated in an orderly way so that each reinforces, supports or complements the others and operates according to an agreed-on plan. Without such coordination the physician in the hospital and the physician in the clinic may give conflicting advice; the volunteer friendly visitor may "baby" the very patient in whom the social worker has been valiantly

trying to develop self-reliance, the public health nurse and the nutritionist may both discuss food budgeting while neither one discusses food preparation or the patient's special problem of coping with inadequate dentures. Without a central plan the family may be confused and frustrated by the many seemingly or actually unrelated actions or directions of the several people involved in the care of the patient. One nurse counted 27 different persons who had rendered some significant service to a hospitalized patient during one 24-hour period.

Achieving a singleness of approach while using a multiplicity of workers is no small administrative task, even if all question of cost is disregarded. If 27 different people are involved in direct contact with a patient, 27 people must know, in varying degrees of technical depth, about the patient, his illness, and the rationale of treatment. If the instruction of a young mother in baby care is provided by the physician, the nurse in the hospital, the instructor in a Red Cross class and the public health nurse—not to mention the health column of the daily paper!—someone must represent a coordinating and synthesizing force to bring order out of the welter of information. When the problem is still further complicated by a patient-load that exceeds the capacity of the staff assigned to provide care (as is the case in nearly every hospital, community agency and physician's office), synthesis requires the utmost in ingenuity and managerial skill.

The following discussion will indicate some of the problems that arise in team care, and suggest some principles for, and practical approaches to their solution. Five major problems have been selected, although they certainly do not constitute a comprehensive list.

FIVE PROBLEMS OF TEAM CARE

1. Inadequate distribution of services

Team services for the long-term and aged patient tend to be organized in medical centers, and within home-care services that may be established in community health agencies. Although such programs are developing rapidly, there are still many areas where no program is available. Furthermore, there is sometimes no service available on an individual basis—for use by the private physician in the care of his patients. This problem cannot be resolved without the initiative and support of the physician himself. It is understandable that the harrassed doctor finds it difficult to attend planning conferences concerning the care of the patient, or to accept membership on planning committees, or to stop in at the hospital or the Visiting Nurse Association to see whether they can help him with particular patients. He struggles alone to interpret dietary measures to a diabetic patient, when the nutritionist or public health nurse from the health department might provide the necessary instruction and supervision. He may fail to secure maximum restoration of physical functioning in a patient because he did not realize there was a physical therapist available from the Visiting Nurse Association. On the other hand, planning groups must take cognizance of the place of the general practitioner and family physician in medical care, and develop new administrative patterns that will allow for combined community-private physician efforts on behalf of the geriatric patient.

2. Lack of cohesiveness in the treatment plan

Duplication, overlapping and confusion in the services afforded may arise. The patient's history, for example, may be taken by several workers, with much of the information duplicated several times. Doctor, nurse, rehabilitation worker and social worker may discuss with the family of a patient being transferred to home care, the nature of the rehabilitation program for this particular patient—each with just enough difference to be confusing. Sometimes there may be actual contradiction in the advice given. Referral plans, designed to provide continuity of care for the patient as he moves from his home to the hospital and back again, may work well in the wards and break down with the private hospital patients, or work well between agencies but not with private practitioners. The public health agency and the hospital may propose different approaches to care; the private physician's opinion may differ from that of the hospital or clinic staff.

3. Unsatisfactory or inadequate service output

In some instances, despite a great deal of service effort, the patient and family appear to have benefited very little. Treatment omissions, errors and delays are reported—for example, hot soaks ordered every hour actually given twice a day, or patients with an order for "no fluids" receiving water from an aide. Inappropriate application of orders may be just as serious—the patient who is allowed out of bed may be permitted to get up too soon after a particularly tiring treatment. Such errors are more apt to occur when several people share responsibility than when one person does everything.

Sometimes the use of multi-personal approach interferes with the full development of the patient's or family's own capacity for health care. The patient with a colostomy may be taught self-care by the professional nurse. However, the teaching may be reduced in effectiveness because the nurse does not come to the patient as someone he has learned to know and trust as she rubbed his back or helped with his feeding.

4. High cost of time

The total time needed to provide care to a given number of patients or families tends to increase when the number of people providing the care increases. For example, if a single nurse provided all of the nursing care needed over an eight-hour period by a particular patient, the total time required to give care would be less than if the same amount of care were given by 6 different workers. More time would be needed for transferring information from one worker to another—reading the record, checking the patient's condition, and so forth. Each worker needs some time to introduce herself to the patient, and to establish a relationship with him. Furthermore, case planning means taking the time not only of the head nurse or public health nursing supervisor and of the professional nurse involved, but also of each of the several individuals concerned, who must understand their place in the total plan and pass on to the planners the results of their activities or observations.

Specialization of workers' functions may also result in some additional time requirements. Both social worker and physical therapist may find it necessary to visit in the patient's home because of the specificity of the things they want to observe, with consequent double travel time. The pattern of having a "nursing interview" following a physician's visit to a patient may decrease the instruction given by the physician, but probably either the nurse or the physician could do both jobs at once. The ward aide who distributes drinking water and has a few other designated tasks may have periods when she has little or nothing to do because the span of her responsibility is so narrow. Recent studies have shown a substantial amount of such "standby" time.

Training costs, too, are apt to be high since effective team functioning demands that all involved have a clear understanding of the operation as a whole, and an appreciation not only of their own tasks but of those of workers with related functions as well.

Communication costs—the cost of time necessary for case planning conferences, referral procedures, inter- and intra-agency reporting—may soar. The paper-work load may also increase.

5. Lack of satisfaction for the patient

A recent patient in a large teaching center where team care was used said, "Everyone knew what they were doing, but no one knew about *me*"; another one said, "I didn't feel any sense of belonging—it was as though I had lost my identity entirely"; still another, "Every time I settled down someone else came in for something—the student nurse with the thermometer, the interne with the needle, the nurse with the medicine, the practical nurse to bathe me, the aide to bring me water. I couldn't remember their names or who did what; it was certainly no rest cure."

Despite these problems, there is no question that the team approach is here to stay, and that as home-care programs grow this approach will likely characterize private medical practice as well as institutional practice. The problem is, therefore, to develop principles on which team care may be based, that will minimize these inherent difficulties and increase the effectiveness of the care. The principles proposed here are not to be considered all-inclusive.

EIGHT PRINCIPLES FOR TEAM CARE

1. The number of individual workers with whom the patient or family is expected to develop a significant therapeutic relationship should be kept as small as possible.

This does not mean that there may not be a relatively large number of people involved in the patient's care. For example, in a hospital there may be any number of persons involved with incidental aspects of a patient's care. The maid who fills the water pitchers; the "lifter" in a nursing home who helps the nursing attendant get the patient in and out of bed; the technician who draws blood for a laboratory test; the nutritionist who figures the proper diet; the head nurse who coordinates the services for the group of patients as a whole;

the attending physician, resident, interne, medical clerk; the ward clerk who takes messages; the transport aide who takes the patient to the x-ray room; the social worker who maintains liaison with the home; the chaplain who provides spiritual support; and the volunteer who brings reading materials or provides friendly services are only a few of those who may be involved.

We need all of this army if care is to be given in adequate quantity and quality to enable the patient to benefit from his hospital stay. However, it is not necessary for each one of these workers to play a significant therapeutic role—to be an active participant in influencing the patient's feelings and actions in relation to his health care.

Whenever possible, services should be channeled through a small group who represent "my" doctor, "my" nurse or "my" welfare worker to the patient. For example, if the nutritionist can, through conference with the nursing staff, transmit information to the patient indirectly rather than directly, the patient is saved the emotional cost of establishing a separate relationship, of learning to know and communicate with another worker. The nutritionist need not take the time necessary to analyze the many-faceted problems of the patient as they affect his diet—his national diet, cultural or family factors that affect the way he eats, his likes and dislikes, and the facilities he has to work with for preparation and storing of food at home. The nurse has already found out much of this, since it is equally important to her in the selection of nursing approaches. When the nursing problems of the patient are minimal and the social ones grave, such nursing advice as may be pertinent may be funneled through the social worker, who becomes the major helping person in the situation. For example, the social worker might well assist with food budgeting, suggest referral to appropriate sources for medical care, and give counsel—which might otherwise have been given by the public health nurse—in relation to parent-child relationships. When many subsidiary workers such as maids or aides are used, the *significant* agent may still clearly be a single person or two. As an instance, if the doctor makes it clear that he is responsible for the action that will be taken by the medical technician, and prepares the patient for the procedure and to accept the need for it, his role as the principal therapeutic agent is great, and the patient need not depend as much on the technician for support in accepting the necessary procedures. In other instances, the medical technician may assume a major role; for example, if the patient's purpose in seeking care is diagnostic and the diagnostic process is largely dependent upon a great many interrelated tests. Sometimes in long-term illness, an aide or attendant may assume a similar central role in care and become "my" worker to the patient.

2. At least one of those in a significant therapeutic relationship should be available to the patient (or family) in some consistent way.

He should reiterate his responsibility for the patient, provide an opportunity for asking questions or registering complaints, and provide an anchor for the patient.

Although this does not necessarily mean a great deal of time with the patient, it does imply more than casual contacts. It may mean being around at critical

moments, like the English visiting nurse who called her newly discharged hospital patients in the evening because "that's the hard time—just before they go to sleep."

3. The members of the team should be united through a common philosophy of service and the acceptance of common goals.

Time should be taken to discuss and agree upon the philosophy with which service is rendered, and what outcomes are expected or hoped for. Such discussion need not be academic in nature; case conferences provide an admirable way to clarify the bases and purposes of service on which specific case decisions must rest. Conflicts in what different workers expect may be brought out in discussing differences between "helping" and "developing independence," between "case selection" and "meeting community needs," between "comprehensive care" and "meeting the need." Sometimes the specific goals of the physician and of the nurse or social worker may be quite different, though all want to improve the patient's health.

4. Judgments that require joint decision by a group of the team members should be identified, and a procedure established for handling them expeditiously.

For example, certain cases will obviously require a careful balancing of judgments and decisions by several workers before a good decision can be reached about recommending home care or setting up a rehabilitation program. In others, with proper routine exchange of information, each worker can proceed in accordance with the general plan for care. The physician may need to decide whether a patient can manage stairs before the social worker can assist the family in their plan for a father to live in his daughter's home. In this case, group discussion may not be needed; the doctor may provide a simple statement in his notes that will guide the social worker, or he may be asked by memo to advise. However, if the daughter is enthusiastic about having her father home but is already overfatigued and responsible for several small children, or if the strength of the father's motivation is not known, a full-scale conference, providing the opportunity to pool the knowledge and judgment of the members of the team, may be indicated. This is the most expensive way of securing a combined judgment but, when actually indicated, it may be the most efficient procedure since it may prevent misdirected effort.

5. Decisions not requiring group judgment should be made by those nearest the first-line worker, and be centered in one person whenever possible.

For instance, how many and which workers are needed to decide whether a patient being discharged from a hospital or nursing home needs the follow-up care of the public health nurse? Is it really necessary to have the physician and the social worker involved in this decision unless there are unusual circumstances, or could it be handled directly by the nurse responsible for the patient without other clearance? Does this decision require the competence of the social worker and the doctor?

6. Group case planning and evaluation may be undertaken for a representative group of patients rather than on an individual basis, if warranted by case similarities.

If selected cases rather than the majority of cases are reviewed by the team,

it will be possible to provide for fuller and deeper exploration of the particular situation. From this comprehensive look, agreements and understandings may be arrived at that will greatly influence the quality of the service, and will provide the groundwork for planning and evaluation by individual workers.

7. Communication procedures should be reviewed for maxium efficiency.

Do forms require copying, or could interleaved pre-set carbons be used? Are the interchanges sent so they can be incorporated into the receiving agency records without copying—on gummed paper, for example? Are telephone contacts grouped to reduce the time consumed? Are volunteers or clerical workers used as far as possible to minimize use of professional time? Are there possible "shorthand" means of recording or reporting? For example, are the same orders copied for 90 per cent of the maternity patients referred? If so, could these be referred to as "standard orders" unless some modification is indicated? Although individualization of problems is great with the older age group, is it still possible that some of the matters involving communication could be defined by a general policy which could be substituted for a one-by-one communication?

8. Respect and mutual confidence among the various workers is fundamental to a good team relationship.

Good team operation is not possible if the physician feels that he must give all the orders, if the nurse feels that social work is unnecessary, or if the psychologist feels that nursing is not really a profession. Opportunities to share experiences, to work out problems together, and to discuss cases and the potentials for service in a deliberative way, will do much to overcome barriers growing out of professional isolation or misunderstanding of professional roles.

COMMENT

The team concept is one of the most significant contributions to geriatric care today. Its application is of particular importance to the family physician if he is to take full advantage of the many services available to him for care of the patient. Only as we learn to use our combined efforts wisely and effectively can we secure the best care for the most important team members of all—the patient and his family.

GERIATRICS, GERONTOLOGY AND GASTRO-ENTEROLOGY.

A Challenge to the Clinician*

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INTRODUCTION

The gastro-intestinal tract along with the liver is almost unique in its ability to reproduce itself. It never wears out (1). It functions throughout senescence with such a vast reserve that it never becomes decompensated and it retains a functional reserve so great that any impairment of function is relatively insignificant (2). There are, therefore, no specific diseases of the digestive tissues which can be ascribed to a wearing-out process. The digestive diseases of the aged are the same as those seen in earlier periods of life, with minor modifications (1), and differences in symptoms are mostly the result of changes in other systems of the body. Primarily, they are the result of changes in the central nervous system and the cardiovascular system, each of which does wear out, and neither of which has the ability to regenerate. The central nervous system repairs itself with gliosis; and the cardiovascular system repairs itself with fibrosis. Both processes are degenerative and irreversible. In contrast, the gastro-intestinal tract may recover from seemingly irreversible disease. The following is an example:

Figure 1A shows the roentgenogram (taken in 1944) of the colon in a patient who was critically ill with chronic ulcerative colitis. Both x-ray and proctoscopic findings were interpreted as being irreversible. Figure 1B shows the same colon eleven years later (in 1955), when the x-ray appearance was that of a normal organ. Proctosigmoidoscopy also demonstrated a normal mucosa without any gross evidence of the previous disease.

Since the change in gastro-intestinal symptomatology with aging is mainly due to changes in the cardiovascular and central nervous systems, the balance between these three systems and the effects of aging provide the real basis for an understanding of geriatric gastro-enterology.

The literature bearing on geriatric gastro-enterology is scanty, and individual experience is limited (3). Until now, the problems in this field have belonged almost exclusively to the clinician. Probably they will continue to be primarily his problem, since most of our knowledge in this area has been gained, not from the basic sciences, but from clinical research.

The reasons for the paucity of information provided by the basic scientists are evident. The biochemist cannot differentiate between a mature cell and an old cell, even in aged and degenerating tissue, let alone in tissue which can regenerate and grow and which has the potential capacity for functioning beyond the ordinary life span. The biochemist not only has no means of differentiating

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FIG. 1. **A**. The colon of a patient with chronic ulcerative colitis; the changes are seemingly irreversible.

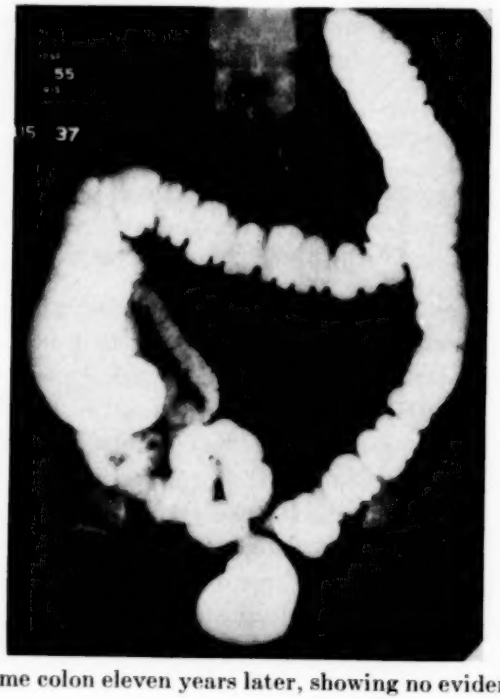

FIG. 1. **B**. The same colon eleven years later, showing no evidence of disease.

the mature cell from the old cell, but he has no methods of approach which give promise of helping him in the future. The physiologist and the pathologist are similarly handicapped. At the tissue level, they cannot determine the age of an organ or tissue, even in areas of degeneration.

Until disciplines are developed to provide a better insight into the nature of the aging process, we must look to clinical techniques of investigation for knowl-

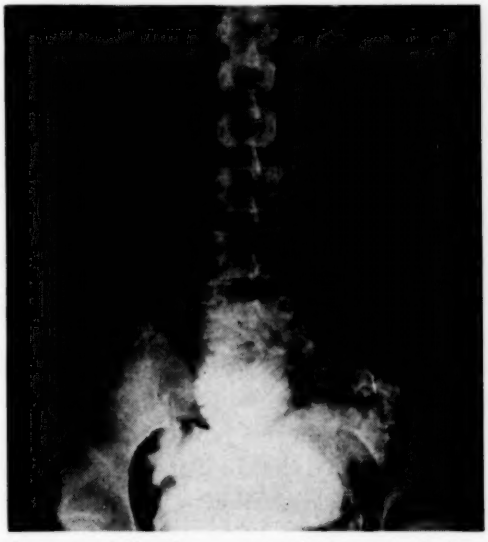

FIG. 2. Functional adequacy following removal of most of the gastro-intestinal tract. Barium can be seen in the stomach following the administration of a barium enema for x-ray examination.

edge regarding the nature and treatment of geriatric gastro-enterologic disorders. The following is an example bearing on the evaluation of function of the digestive mechanisms:

Figure 2 illustrates the functional adequacy of the gastro-intestinal tract following removal of all but 12 inches of the jejunum, all of the ileum, all of the cecum, and the proximal half of the colon. In a barium x-ray examination, the barium flowed immediately into the stomach. While the patient was in the hospital, nutritional balance was maintained and there was no evidence of nutritional deficiency or avitaminosis.

STRUCTURAL AND OTHER CHANGES INCIDENT TO AGING

There is no intent to imply that the gastro-intestinal tract is not affected by age; it is, but not because of disease of the digestive cells. In association with deterioration of the structural tissues of the body, there is a tendency towards herniation; this may or may not be symptomatic. In addition, the incidence of cholelithiasis increases with age; this condition is largely asymptomatic. In 1924 Graham and Cole demonstrated for the first time a technique whereby the gall bladder could be visualized roentgenologically (4). Since then, an increasing amount of x-ray data has become available for interpretation. More recently, the type of examination for executive personnel has become popularized; visualization studies of the gall bladder usually are included. We may anticipate an ever-increasing number of patients with chronic asymptomatic cholelithiasis. Sklar, Kirsner and Palmer in 1956 reported cholelithiasis in 7.7 per cent of 300 patients past the age of 65 (1). Surgery was performed in 14 of 23 symptomatic cases, but only 8 were completely relieved of symptoms.

Ivy and Grossman (2) looked upon thinning of the colonic musculature with advancing age as a cause of the increased incidence of diverticulosis. Diverticu-

losis occurs predominantly in the sigmoid and has been described by Snell (3) as being as common as gray hair or wrinkles after 50 years of age. Sklar and associates (1), however, found it in only 20 per cent of their 300 patients past 65 years of age. It has been demonstrated that there is no correlation between the incidence of carcinoma and diverticula of the colon (5), just as there is no correlation between the incidence of hiatus hernia and of gastric or esophageal carcinoma (6).

Hiatus hernia is another condition found with increasing frequency, not only because of the increase in number of elderly persons, but also because of increased proficiency on the part of the roentgenologist. The incidence varies widely. Portis and King (7) noted an incidence of 7.5 per cent in 133 patients ranging from 60 to 83 years of age, but Brick (6) found an incidence of 76.6 per cent in his series of patients between 50 and 80 years of age. With such a wide discrepancy in the information regarding the incidence, one may question the clinical significance of the finding in most instances. In our own institution, the roentgenologist believes that the finding of a hiatus hernia may confuse the clinical picture rather than clarify it, and opines that "It would be better, in most instances, had the condition not been found."

Cholelithiasis, diverticulosis and hiatus hernia occur so commonly in the aging population that they have been grouped together as a triad. It is commonly referred to as Saint's triad, after Professor Saint of Capetown, South Africa, who in 1948 noted the frequent coexistence of the three conditions (8). It is noteworthy that these conditions, for the most part, are asymptomatic. Thus, when symptoms do occur, it is important that they be attributed to the proper organ. The clinician should recognize the high incidence of all 3 conditions and the infrequency with which any of them causes symptoms.

In view of the relative infrequency of disease of the gastro-intestinal tract in the aged, the atypical manner in which symptoms occur, and the problems presented by mental deterioration, vascular change and other factors, the importance of Saint's triad is relatively insignificant. The functional complaints of the aged are legion, even in persons who have an organic disorder. Therefore it is necessary to differentiate a patient's presenting symptoms, not only from those of the triad, but also from some other types of functional or organic disorders (9, 10).

SYMPTOMATOLOGY OF GASTRO-INTESTINAL CONDITIONS—CONSTIPATION

Of the symptoms necessitating medical aid, those referable to the gastro-intestinal are the most frequent, beginning in infancy (11) and increasing with advancing years. The outstanding difference between the symptoms of the same disease in the geriatric patient and in the younger patient is the tendency toward atypical symptoms in the elderly (3). Therefore, it is extremely important to subject the elderly patient to a thorough examination, in order that asymptomatic pathologic conditions may be discovered.

Major complaints referable to bowel habits and to constipation, real or fancied,

are usually lifelong. If of less than five years' duration, they should be looked upon with suspicion as probably due to malignancy. To a significant degree, the symptomatology as presented to the physician by the geriatric patient may reasonably be attributed to changes in the central nervous system or the cardiovascular system.

The importance of common proctoscopic observations should be emphasized. Not infrequently, upon proctoscopic examination of the elderly patient, one sees a dehydrated rectum and sigmoid colon; there also seems to be a decrease in the secretion of mucus. It is impossible to correlate any such observations with bowel function, but the implication is that the colon of the older patient is less well lubricated than that of the younger. A common handicap in proctoscopic observation is the presence of undigested food in the rectosigmoid colon which has been inadequately prepared for the examination. No clinical significance should be attached to this finding because there is no association with nutritional deficiency. It simply indicates the tremendous physiologic reserve of the digestive tract.

Much has been written on the treatment of constipation, especially in the aged. Mental and other central nervous system changes may be the most important considerations in the treatment of constipation in the aged. Therefore, these patients should be treated individually. This is another opportunity for application of the art rather than the science of medicine.

THE COLON

Diverticulosis is common after the age of 50 and is usually asymptomatic. It becomes symptomatic when the patient becomes aware of it. Symptomatic diverticulosis, therefore, is primarily an iatrogenic disease. Diverticulitis, on the other hand, is a rarity—at least in private practice (3). Sklar and associates found diverticula in 60 out of 300 patients, but diverticulitis in only 9 (1).

Chronic ulcerative colitis, so lethal in the college student, is not only rare in the aged but is mild and limited. Less than 2 per cent of cases occur after the age of 60 (12).

The importance of neoplasia among diseases of the gastro-intestinal tract in the aged is indicated by the fact that carcinomas of the stomach, liver, gall bladder and bile ducts comprise one-third of all carcinomas and are the cause of 2.6 per cent of all deaths. Fifty per cent of all carcinomas are of gastro-intestinal origin and account for more than half the deaths due to disease of the gastro-intestinal system in patients past 45 years of age (13). Proctosigmoidoscopic examination is most important. When carcinoma of the stomach is discovered, it is usually too late. More than 50 per cent of gastric carcinomas are found either post mortem or terminally.

In our recent study in which we compared the relative values of barium x-ray examination of the colon and proctosigmoidoscopy (Tables 1 and 2), we found five times as much neoplasia by proctosigmoidoscopy than could be demonstrated by barium x-ray examination (14). Table 2 illustrates the advantages of proctosigmoidoscopy.

TABLE 1

Results of Barium-Enema X-ray Examination in 881 Patients

Lesion	Number of Cases Found by	
	14 x 17 in. roentgenogram*	70-mm. photo fluorogram†
Significant	3 (1.2%)	6 (0.9%)
Benign polyp	1	2‡
Malignant polyp	2	2
Annular carcinoma		1
Submucosal lipoma		1
Suspected	17	31
Not found by regular barium enema	12	23
No follow-up	5	8
Other	41	75
Diverticula	40	73
Anomalies of rotation	1	2

* No. of patients examined = 243.

† No. of patients examined = 638.

‡ One other patient had a polyp in the transverse colon that was confirmed by several barium enemas, but no operation was performed because of extensive carcinoma involving the neck glands.

TABLE 2

Significant Findings in 701 Proctosigmoidoscopies

Lesions	Number of Patients*
Benign polyps	21
Malignant polyps	11
Polyps, histology unknown	3†
Carcinoma of anus	1
Total	36 (5.1%)

* Six patients had multiple polyps (usually two), in only one of which were malignant changes found.

† Pathologic findings not obtainable.

Because the patient tends to believe that all symptoms referable to the anus are due to piles—itching, bleeding or protruding—pathologic conditions of the anus are thought to occur much more frequently than actually observed upon routine examination in a proctoscopic clinic. The characteristics of the anus in the elderly, in contradistinction to those in youth, are the increase in redundant skin with the formation of tags, and the tendency toward prolapse of the rectum. This develops concomitantly with the difficulty in maintaining cleanliness of the area, and emphasizes the inadequacy of toilet paper alone in achieving anal cleanliness. Washing with water is necessary, even if the water has to be taken from the freshly flushed toilet bowl or tank in case of emergency.

THE UPPER GASTRO-INTESTINAL TRACT

A common reason for seeking medical advice is one of the multiple symptoms referable to the upper gastro-intestinal tract. These symptoms are largely of a functional nature.

The esophagus presents no evidence of aging and has the sole function of transport, yet it is perhaps the most "vocal" organ of the upper gastro-intestinal tract. Many symptoms attributable to the stomach are obviously of esophageal origin, *e.g.* heart burn. In this area, therefore, there is no particular clinical problem incident to aging.

It is difficult to evaluate changes in intestinal transport which might be attributable to motor disturbances in the aging patient. The passage of material from a test meal may take from twenty to seventy-two hours in a normal person, and vestiges may remain for as long as seven days. There are no data on elderly patients to correlate with these normal figures (15–17).

Secretory changes in the stomach are most important, but not as a geriatric problem. Physiologically, the secretion of hydrochloric acid decreases with aging. The presence or absence of free hydrochloric acid is of no clinical significance insofar as gastric digestion and symptomatology are concerned. A patient with the so-called hyperacidity syndrome may experience relief as readily from the administration of dilute hydrochloric acid as from soda. What is important, however, is that the incidence of peptic ulcer changes with aging. Sklar and associates pointed out that, whereas the incidence of active peptic ulcer remains relatively constant (10 per cent in patients past 65), the ratio of duodenal to gastric ulcer does not. The ratio of duodenal to gastric ulcer changes from 8–10:1, to 2:1, thus approaching autopsy ratio of 1:1 (1). This relative increase in the incidence of gastric ulcer with age, along with an increased tendency of gastric ulcers to bleed due to arteriosclerosis, can account for the progressively higher death rate with advancing age up to 75 years in both males and females (13). This is in contrast to duodenal ulcer, which does not show much change in incidence beyond the fifth decade. However, the increase in death rate with advancing years can be accounted for mainly by the increased lethality of the major complications of peptic ulcer. Hemorrhage and perforation constitute the greatest hazards. Hemorrhage is not only lethal, but it occurs more often in the aged. The later the onset of ulcer, the greater is the tendency to bleed. Although gastric ulcer is more asymptomatic and occurs less often than duodenal ulcer, gastric ulcer causes death more frequently (18).

SUMMARY AND COMMENT

The tissues of the digestive tract have the unusual ability to reproduce themselves by regeneration of cells and reconstruction of tissue. Recovery from disease can take place after seemingly irreversible changes. Aging, therefore, is not a characteristic of digestive tissue or its cells. The gastro-intestinal diseases of the aged are the same as those of younger patients.

Functional changes with aging, such as increasing anacidity, are not a clinical problem. Constipation, the most frequent functional disturbance in the infant,

is also the most frequent complaint of the aged. Malignant tumor is the most important organic disease.

There is a close interrelationship between three body systems: the gastro-intestinal tract (which does not wear out) and the central nervous system and the cardiovascular system (which do degenerate and wear out). A continuing change in the balance between these systems largely accounts for the problems of geriatric gastro-enterology. The digestive tract, which does not age, lives in an aging body.

These alterations with aging present problems which extend beyond the scope of medicine into the broader field of gerontology. The basic biologic differences between human beings may be particularly evident in the very old. By virtue of having reached the eighth decade, they manifest better biologic material than some of their juniors. Many diseases, such as cirrhosis of the liver, have passed their peak incidence as a cause of death by the time people have reached the age of 60.

The classic statement regarding the afflictions of the aged in the twelfth chapter of Ecclesiastes begins: "Remember thy Creator in the days of thy youth, before the time of affliction come . . . ." It is significant that the only allusion to infirmities of the gastro-intestinal tract concerns the teeth: "And the grinders shall be idle in a small number." It is only the teeth that wear out.

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THE LITTLE STROKE.

A Report on 89 Cases*

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In the past, a diagnosis of stroke was made without specification of the etiology, as this was not a primary consideration in the clinical management (1). Today, accurate diagnosis in cases of stroke has become imperative as a prerequisite for adequate treatment (2, 3).

Cerebrovascular accidents are fourth among the causes of death and account for about 200,000 fatalities each year in this country alone. Approximately 800,000 additional persons are partially or totally disabled by such accidents (4). Clinical and pathologic reports over the past several years leave no doubt that segmental atheromatous occlusion of the cervical carotid artery is the cause of approximately 1 out of every 4 strokes (5). In three-fourths of all cases of stroke, there is cerebral hemorrhage of varying degrees of severity. Angiography is being increasingly employed for determining the etiology and confirming the diagnosis of stroke. The importance of these differential data is underscored by the fact that although anticoagulants are indicated in the treatment of arterial occlusions associated with cerebral arteriosclerosis, they are contraindicated in the hemorrhagic type of stroke.

In the present study, only the problem of so-called little or small stroke was investigated. During the last six years, 89 cases of little stroke were observed and treated with water-soluble bio-flavonoids—factors that are effective in restoring capillary integrity and decreasing capillary fragility.

CLINICAL SYMPTOMS OF LITTLE STROKE

The little stroke is very common. It is estimated that in this country alone there are about 1,200,000 living persons who have had one or more small strokes (4). The symptomatic manifestations and their severity vary considerably. In many cases, one small stroke is followed by another at short intervals, eventually ending fatally. In other cases, several years or more may elapse before a second attack occurs. As a rule, the first incident is very mild and may pass unnoticed by the patient or his physician. There may be no signs of weakened muscles, no trouble with speech, and no area of anesthesia. The patient may suffer only from changes in character, ability, judgment, or emotional stability. In still other cases, there may be temporary hemiplegia, monoplegia, hemianesthesia, aphasia and visual disturbances.

On clinical examination and cerebral arteriography, no occlusions can be

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detected in most cases. When hypertension is not present, the prognosis is better (6).

The following case of a college professor is typical of the course of this condition:

> The professor, 66 years old, was a man of dynamic personality, and was powerful, physically and mentally. There was nothing medically wrong with him until six years previously when, after finishing a lecture, he experienced a strange sensation. One of his arms became numb and he was unable to talk. This sensation was very brief, lasting hardly fifteen minutes. He soon regained his speech and the movements of his arm. For the next three years, he continued to live energetically, writing, traveling and lecturing as before. Three years later, he suffered another little stroke, but this time much more severe. For two weeks, he was in a hospital with his left side paralyzed, and his speech affected. He recovered from the second stroke, a changed man—nervous, easily tired, and unable to concentrate his thoughts on any subject. Two years later he had a third stroke which left him unable to speak or to walk, with his mind seriously affected.

The case of a late President may also be cited as a classic example. During the last eight years of his life, he had six incidents of little stroke, each time more serious, with the last being fatal.

Little strokes occur mostly among the middle-aged and elderly. However, a number of cases in young people have been described. Stevens (7) reported 32 cases of previously healthy normotensive young persons between the ages of 5 and 45 years who had little stroke with acute hemiplegia and other focal neurologic manifestations. Daws (8) and others reported similar cases. Skinhøj (9) stressed the fact that the case fatality rate is higher in comparatively young patients than in older ones, presumably because of hypertension and chronic nephritic complications.

ETIOLOGY OF LITTLE STROKE

The etiology of little stroke has long been a controversial subject. In the past, the opinion prevailed that the cause is cerebral angiospasm. The presumed presence of cerebral angiospasm was the basis for treatment by anesthetizing the stellate ganglion (10). This procedure was supposed to abolish or prevent cerebral vasospasm by blocking the vasoconstrictive impulses to the affected vessels. However, it has been postulated that anesthetization of the stellate ganglion improves the cerebral circulation by its effect on the systemic circulation, rather than by abolishing spasm of the intracranial vessels. This controversial problem was resolved by the work of Pickering (11) and Rothenberg and Corday (12). Pickering demonstrated that cerebral arteries lack vasoconstrictor innervation and musculature, so it is difficult to understand how constriction of these vessels (angiospasm) can occur. He suggested, rather, that little stroke is caused by minute hemorrhages from the cerebral capillaries. Rothenberg and Corday, of the University of California, investigated this problem experimentally in Rhesus monkeys. They, too, concluded that "cerebral angiospasm does not occur. Cerebral strokes are due to cerebral vascular insufficiency, thrombosis or hemorrhage."

In order to understand the factors involved in little stroke, it should be pointed out that there are no effective channels of collateral circulation between the various terminal arterial branches supplying parts of the brain. This absence of collateral circulation is compensated for in the brain tissue by an extensive capillary network. Moreover, the regions of the brain with the greatest neural surface areas are more vascular and have a more extensive capillary network [Magoun (13), Wolff (14)]. All these recent data indicate that cerebral activity and cerebral disturbances are related to the level of capillary function, emphasizing the importance of capillary injury as a principal etiologic factor in cerebral dysfunction.

These postmortem findings have been confirmed by the pathologic studies of the brain of persons who have succumbed from little stroke. Thus Wartman (15), confirming Paterson's (16) findings, stressed the fact that in atheroma, bleeding occurs from the capillaries of the intima of blood vessel walls.

From extensive histopathologic investigations of persons who died from apoplexy, Paterson (16) concluded that "intimal hemorrhages in cerebral arteries result, not from backflow of blood through defects produced by rupture of atheromatous abscesses as was previously thought, but from rupture of capillaries derived from the main arterial lumen." Adams (17) stressed the prime role played by the cerebral capillaries in the re-establishment of proper circulation, which is essential for recovery from apoplexy. Scheinker (18) described the vascular changes of the brain regularly observed in cases of cerebral hypertension. "The early stage is characterized by increased cellularity of the small capillaries. These changes are seen in cases which survive arterial hypertension for about a period of one or two years. The vascular changes are confined to capillaries and small arterioles . . . . The gross appearance of the brain in chronic cases of arterial hypertension is characterized by a large number of small areas of softening. Since only the small blood vessels are involved in the pathologic process, only small areas of cerebral parenchyma are destroyed. The transient nature of some of the neurologic symptoms might be best explained by the smallness of the cerebral lesions." This may also explain the fact that in little stroke the clinical symptoms may subside within hours or days. Similar data were reported by Hughes and Parker (19). Postmortem examination of persons who died from little strokes showed that in each case there were multiple foci of softening involving the subcortical centers, including the *caudate nucleus* and *putamen*. These were always found in the areas of perforating small arterioles and capillaries. As Barr (20) emphasized, in the majority of brain infarcts there are no discoverable organic occlusions and the lesions are attributed to local functional circulatory disturbances, in which capillary dysfunction and injury seem to play an important role. Westphal and Baer (21), Stern (22), and Scheinker (18) expressed the belief that cerebral hemorrhage results from bleeding of injured blood vessels, arterioles and capillaries. Hicks and Black (23) carefully studied 155 cases of cerebral infarction and found only 33 clearly attributable to thrombus. In the rest of these cases, there were no arterial occlusions—from thrombosis, atherosclerosis, or any other discernible cause. *The over-all picture*

of these histo-pathologic findings emphasizes the essential role that capillary injury plays in this condition, and substantiates the work of Pickering (11) and Rothenberg and Corday (12), that angiospasm is not the underlying factor in little stroke.

CAPILLARY FRAGILITY AND CAPILLARY TOXICOSIS

The capillary system, which plays an essential part in the exchange of body fluids and in circulation of the blood, is highly susceptible to toxic influences, both endogenous and exogenous. Mueller (24), Davis (25), Beaser *et al.* (26) and others found a high incidence of increased capillary fragility among patients affected with various chronic diseases such as diabetes, arteriosclerosis, hypertension and rheumatoid arthritis. In bacterial and viral infections, localized or generalized capillary toxicosis with minute hemorrhages was often observed, particularly in infectious hepatitis (27, 28), smallpox (29), St. Louis encephalitis (30), influenza A virus (31) and other infections. Bacterial endotoxins injected intradermally or intravenously into rabbits induce capillary toxicosis with capillary hemorrhage, according to Fujisawa (32). Excessive cold or heat may also result in increased capillary fragility, as reported by Zaprometov (33). Increased capillary fragility is a frequent phenomenon in aging persons, as shown by Perry and Linden (34), Martin (35), Sokoloff *et al.* (36) and others. The frequency of stroke among the older population, particularly among those with chronic diseases, and the fact that the stroke often occurs soon after a viral or bacterial infection strongly point to capillary injury as the major factor in causing little stroke.

EFFECT OF BIO-FLAVONOIDS ON CAPILLARY FRAGILITY

Since Albert Szent-Györgyi's discovery of "vitamin P," otherwise known as bio-flavonoids, a voluminous literature has appeared on the prophylactic and therapeutic value of these factors in conditions involving capillary dysfunction and increased fragility. Sokoloff *et al.* (37) reported that water-soluble bio-flavonoids prevented capillary hemorrhage in animals receiving injections of bacterial polysaccharide. Fujisawa *et al.* (38) found that the water-soluble flavonoid compound known as C.V.P. prevented inflammatory reaction and capillary hemorrhage in rabbits given oncostatic and other antibiotics. Menkin (39), in an extensive investigation of the properties of the same C.V.P. compound, observed that it prevented inflammatory reaction and accumulation of dye in rabbits given injections of leukotaxine or inflammatory exudate. In a series of independently conducted investigations, workers in the U.S.S.R. reported the therapeutic value of bio-flavonoids in capillary fragility and hemorrhage—Zaprometov (33) in capillary toxicosis induced by antibiotics and sulfa drugs; Chamrai *et al.* (40) in hypoxia due to exposure of animals to rarefied air; Pankratkoff (41) and Litvak and Chklovsky (42) in clinical capillary toxicosis in adults and children caused by antibiotics or bacterial and viral infections; Rosentul *et al.* (43) in persons who worked in the excessive heat of steel plants or in winter cold; and others in various pathologic conditions with capillary hemorrhage complications. Sokoloff *et al.* (36, 44) reported the salutary effect of water-soluble bio-flavonoids

in the treatment of little stroke. This therapy, in continued use, reduced the number of recurrences in the patients so treated compared to the number in untreated patients of a control group.

CLINICAL STUDY

Clinical material and methods

Patients. In cooperation with a group of physicians, 89 cases of little stroke were treated with a water-soluble bio-flavonoid preparation combined with ascorbic acid (C.V.P.[1]). As a control, 62 cases of little stroke treated by other therapeutic measures were observed by the same group of physicians. Only cases of cerebral hemorrhage were included in either group. All cases of cerebral arterial occlusion, either suspected on the basis of the neurologic symptoms or verified by cerebral angiography, were omitted from this study. The average period of observation, and the age and sex of the patients in both the C.V.P. and control groups were as follows:

	Bio-flavonoid Group 89 cases	Control Group 62 cases
Sex:		
Males	65	44
Females	24	18
Age:		
41–50	22	15
51–60	30	20
61–70	27	19
71–85	10	8
Period of observation:		
4 years or more	22	8
3–4 years	23	15
2–3 years	23	12
Less than 2 years	21	27

Hypertension was present in 32 patients of the treated group and in 23 of the control group. There were 10 cases of diabetes of long duration in the first group and 5 in the control group. Mild arthritic manifestations were observed in 27 of the treated patients and in 20 of the controls. There were 2 cases of pernicious anemia in the treated group, and 1 in the control group. Thirty-three persons in the treated group and 23 in the control were unaffected by any other chronic diseases.

Capillary fragility tests. All patients were routinely checked for capillary fragility, by applying a negative pressure of 30 cm. of mercury to a circumscribed area of the skin. The degree of capillary fragility as measured by the number of petechiae varied considerably, from 5 to 50. The hypertensive and diabetic patients showed the highest degree of capillary fragility with the number of petechiae rising to as high as 48–50 per unit area. Since it has been reported (36) that bio-flavonoids have a beneficial influence on increased capillary fragility in older people, the petechial index was rechecked regularly every six months both in the patients treated with C.V.P. and in the control group.

Results

In this series, little stroke was more frequent among men than among women. It occurred more often in the 51–70 age group than after the age of 70, but this

[1] C.V.P. is a water-soluble citrus bio-flavonoid compound containing 100 mg. of bio-flavonoids and 100 mg. of ascorbic acid per capsule. Manufactured by U. S. Vitamin and Pharmaceutical Corporation, New York, N. Y.

observation should be taken with some reservation because of the small number of cases in the study.

Determinations of capillary fragility by means of the petechial index yielded the following results:

	No. of Patients
Bio-flavonoid (C.V.P.) group	
Before treatment; more than 10 petechiae	71
After six months of bio-flavonoid therapy; more than 10 petechiae	21
After twelve months of bio-flavonoid therapy; more than 10 petechiae	15
Control group	
Initial count of petechiae, more than 10 per unit area	52
After six months; first reading	48
second reading	51

The data indicate that C.V.P. had a markedly beneficial effect in moderating the severity of capillary fragility, although in a number of patients the response was only partial.

Results of the tests in patients of the control group receiving no C.V.P. therapy indicate that capillary fragility remained more or less stationary.

All the patients, whether C.V.P.-treated or not, had had from one to four little strokes before the C.V.P. treatment was initiated in the treatment group.

The following 2 cases are typical examples of the response to bio-flavonoid therapy:

A. B. L., a lawyer 53 years of age, was very active in his profession and had no chronic diseases, but was living under constant nervous stress. In September 1955, returning home from his office, he experienced a strange sensation, as if he were fainting, associated with numbness of his arm. In twenty minutes or so this sensation had disappeared and he paid no more attention to it. In December of the same year, he had a serious attack of influenza A virus infection which kept him in bed for two weeks. Returning to his office, he had a mild stroke, was unconscious for about one hour, and was transferred to the hospital. His blood pressure was 155/90 mm. Hg, but there was no cardiac involvement. Electroencephalographic examination showed a delta focus in the motor region. No cerebral occlusion was detected by angiography. A hemorrhage was detected in the eyegrounds. The pineal gland was in the normal position. The petechial index was 46. Diagnosis: cerebral hemorrhage. In three weeks, the paralysis subsided, and his general condition was greatly improved. In January 1956, he decided to return to his office. A new mild stroke occurred. Treatment with C.V.P. was started in a dosage of eight capsules a day, reduced in three weeks to six capsules a day. He has continued taking C.V.P. to date—four years later—and has had no further strokes. His petechial index is now reduced to 6–8.

H. L. N., the president of a chemical concern, was 62 years of age. In February 1956, he suffered a little stroke with hemiplegia, aphasia, and a visual disturbance. His case was mistakenly diagnosed as cerebral occlusion, and anticoagulants were prescribed. Two weeks later he had another small stroke which kept him in bed for three weeks. In April 1956, he caught a bad cold which continued for several days with fever. On April 15, he had a third little stroke, with monoplegia and hemi-anaesthesia. His blood pressure was 162/88, but there was no cardiac involvement. Moderate arthritic manifestations were present. There was no albumin in the urine. Liver function was normal. The petechial index was 43. It was decided to treat him with C.V.P., ten capsules per day. The daily dosage was reduced to eight capsules in two weeks, and to six capsules in four weeks. There have been no other little strokes to date—four years later. The petechial index is now 5.

A comparison was made of the incidence, severity and deaths from stroke in the 89 patients treated with bio-flavonoids (C.V.P.) and the 62 patients in the control group, followed over periods of one to five years. The results were as follows:

Bio-flavonoid group (89 patients)	Three cases of little stroke; no fatalities.
Control group (62 patients)	Eighteen cases of severe stroke, including 5 fatalities; 12 cases of little stroke.

Thus, bio-flavonoid (C.V.P.) therapy had a beneficial effect in reducing the number of recurrent little strokes. Moreover, this prophylactic effect was correlated with a decrease in capillary fragility.

DISCUSSION

The accurate diagnosis of the type of stroke and an understanding of the underlying factors are prerequisites to the rational treatment of this condition. Once cerebral occlusion is ruled out by angiography, cerebral hemorrhage must be suspected. When the hemorrhage is large, there is little chance to save the patient, except possibly by emergency surgery. The great majority of strokes, however, are caused by minute hemorrhages from small blood vessels, arterioles and capillaries.

The recent investigations of Pickering (11) and Rothenberg *et al.* (12) have proved beyond doubt that angiospasm is not the cause of little stroke, as some clinicians still believe. On the other hand, the highly vascularized nature of brain tissue emphasizes the vital role which the cerebral capillaries play in restoration of the collateral circulation of injured tissue. The pathologic findings demonstrate that embolism and occlusion are relatively rare phenomena in little stroke, and that capillary bleeding is the true and most frequent cause of this condition. The results of the present clinical study lend new support to this point of view, stressing once more the necessity of giving full attention in cases of little stroke to the role of the cerebral capillary system and to rational therapy for repairing its structural defects.

SUMMARY

Eighty-nine cases of little stroke, with a past history of one to four incidents, were treated with a combination of water-soluble bio-flavonoids and asorbic acid (C.V.P.) as factors controlling capillary permeability.

Sixty-two cases of little stroke receiving medications other than bio-flavonoids served as a control series.

About 80 per cent of the patients in both groups initially showed increased capillary fragility. .

Therapy with a special water-soluble bio-flavonoid combined with ascorbic acid (C.V.P.) progressively reduced the proportion of patients affected with abnormal fragility of the capillaries to 17 per cent.

In the group of 89 patients treated with C.V.P., there were 3 cases of little

stroke and no fatalities. In the control group of 62 patients, there were 18 cases of severe stroke including 5 fatalities, and 12 cases of little stroke.

The role of the cerebral capillary system in little stroke is discussed.

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A DIFFERENT APPROACH TO THE TREATMENT OF THE OLDER MALE VETERAN PATIENT

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Geriatrics, according to leading medical authorities, is a carefully detailed study of the process of aging. In the geriatrics program at the Veterans Administration Outpatient Clinic, Brooklyn, N. Y., the prolongation of life is not regarded as the primary goal; the aim, rather, is health in old age.

The unprecedented gain in longevity, mostly due to successes in the battle against infectious disease, has taken the nation by surprise and may cause social crises. Chronologic age, apparently, does not by itself lessen the older person's desire for useful living. It is not enough to live many years. The goal should be long life lived to the end in dignity and security.

Studies of effective use of increased longevity are being pursued. To respect the older person's integrity and his inherent right to self-determination, stereotyped thinking about him must be discarded. Poor health is not necessarily an accompaniment of the aging process. The VA OPC studies indicate that many of the fears and anxieties of older persons are the result, not so much of any physical deterioration, but of changes in their life situations. Some of these changes are:

a. Enforced retirement and inability to secure employment.

b. The resultant economic, emotional and social dependence upon others.

c. The lack of suitable medical, recreational and social facilities.

The OPC is concerned about those attitudes which tend to cause fear of aging and rejection of the aged. Society attaches much importance to productivity or earning power. Prestige and status are often regarded as impossible without employment. Often the older person feels he is a burden when income is reduced. Many find it difficult to manage solely on income from pensions, Old Age Survivors Insurance and/or Public Assistance. Medical care, and pleasures and conveniences that were previously within financial reach must be given up.

The older person may then become conservative, rigid, and critical of the younger generation. He may resort to destructive preoccupation with himself, with resultant exacerbation of physical symptoms of organic disease.

There arises a sense of futility, cynicism or resignation. He may live in the past, recalling earlier achievements and enlarging upon them. Through these defenses he attempts to achieve the feeling of being secure, accepted, and important.

Often illness serves to justify for the older person his diminished accomplishments in life. Illness may be viewed not as an escape from responsibility, but rather as a direct response resulting from repeated frustrations associated with growing old.

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The unprecedented gain in length of life has also resulted in a dynamic increase in requests from disabled (service-connected) World War I and Spanish-American War veterans for services to assist them to cope with their health problems. A heterogeneous group, there are among them people with varied physical, emotional and socio-economic needs.

VA OPC (BROOKLYN) SERVICE PROJECT

To increase knowledge through service, the Manager of the VA OPC, Brooklyn, authorized a service project in which basic professional principles and concepts would be employed in a concentrated team effort to provide more extended care for the older veteran patient. The groundwork for the development of a geriatrics clinic was prepared in 1957 by the establishment of group programs for older disabled (service-connected) male veterans, led by a treatment team composed of an internist, a clinical social worker, and a nurse.

A primary objective in the treatment of the individual veteran in the group is the prevention of illness. The preventive role concerns itself with the predictable physical and emotional problems of old age. As people age, there arise a number of crises in which radical transformations in their life situations occur. These transitions often cause anticipatory fear and intense stress. Some of the stress situations are brought on by incapacitation because of accident or organic disease with resulting enforced dependency, hospitalization and surgery; the death of a spouse; the sudden loss of employment; or reduced income.

It is not known when these trauma will occur, but they are certainly contingencies in the lives of aging persons. By anticipation, and preparation through education, motivation and the development of multiple channels of interests, much of the injury inherent in these vicissitudes of existence can be averted (1). The result of this prophylactic approach can be the prevention or reduction of the damage which may follow these health hazards.

DETERMINATION OF NEED

The basic criterion used in selecting persons for admission to the group was *need*. The preference was for patients 65 years of age and older who had recently faced, who were facing, or who might soon face crisis situations not previously experienced by them.

Since grouping on the basis of age alone has proved to be unsatisfactory (2) each group formed was composed of persons of similar intellectual ability. This was to prevent possible breakdown in the group process because of varied levels and modes of communication among the subjects. It was found that interaction took place at an optimum level in groups limited to a total of 7 to 10 members. All World War I and Spanish-American War Veterans who attended the clinic for medical treatment during selected two-month periods were screened by the clinical social worker to determine their need for, and interest in the program. Once interest in the program was established, the patients were invited to return within several days to a few weeks after the initial (screening) interview for

another social service interview. This second interview was regarded as necessary for several reasons:

a. To evaluate each patient's readiness for, and interest in, participating in the program. Some of these patients when seen for the second time did not really want to participate. Their initial passive acceptance of the program reflected their fear that they would lose their pension if they refused.

b. To introduce these patients to the other team members (the internist and the nurse). Before such introductions were made, each patient's health situation was discussed and his medical records reviewed in conference. Meeting the physician and the nurse helped the potential group member regarding any anxiety he may have felt as he was about to begin a new experience.

GROUP PROCESS

These group sessions provided opportunities for the patients to share past or present experiences regarding common health, home care, employment, finances, shelter, recreation or other problems and, through interchanges in the group, to assist each other. The patient's self-preoccupation lessens when he meets with other people with whom he shares his problems and emotional experiences.

The group is viewed as a natural formation which has definite influence on the individual members. Discovery of how others experienced and coped with a similar problem reduces the individual's sense of aloneness and futility. Activities developing out of expressed or implied interests tend to reduce preoccupation with self and the future.

In view of the fact that the groups were agency-sponsored and the program was new to them, the geriatrics team took an active part in formulating topics for discussion and in eliciting the needs and interests of the members. The leadership role was conceived as an initial aid in getting the members to feel comfortable in the setting.

A way of helping the group to find its own answers was to encourage discussion of common needs and interests, of the agency program of benefits, and of military service experiences, or of their experiences in other groups.

As the groups became stabilized, more responsibility for planning and content was accepted by the members. They selected many of their own goals and developed some of their own program content. Occasionally, after a stimulating meeting, there was a temporary impasse, indicating the need for a rest before another sustained movement could be made.

In the semiformal group setting, the patients found that they obtained guidance, emotional sustenance, and reinforcement. They engaged also in self-expressive activities and experienced the satisfactions derived from participating and achieving.

The learning process was accelerated when the motivation to learn stemmed from interest in specific concrete goals. There were some indications that difficulty in learning was related to awareness of the consequences of making errors.

Once motivated to acquire new skills and knowledge, the patients carried on with minimal assistance.

Much of the pervading tension in the group setting, on the part of the many patients with visual or auditory limitations, was eased when leadership assumed responsibility for recognizing these impairments in a frank and realistic way. As a result, the strain of keeping up with the conversation in the meetings was eased.

Audiovisual tools were of distinct value in educating the patients and stimulating discussion. Visual aids provide perceptual foundations when actual experience is lacking, and enable verbal instruction to transmit these into conceptual products through the processes of interpretation, integration and generalization (3).

Effective use was made of demonstration films and film strips, the latter consisting of a series of related art frames in color. Each strip was designed to help promote the teaching of basic medical, nursing and nutritional facts. Best results were obtained with these audiovisual aids when they were introduced in such a way that the patients could see the relationship between the content of the films and the subjects under discussion. The films, though individually complete, were designed to supplement each other. In conjunction with each film strip, there was a narration on records.

Wall charts and booklets (designed as "take-home items") were used to supplement discussion and film presentations. With the combined audiovisual technique, the patient with either auditory or visual impairment appeared to derive direct and definitive benefit through the utilization of the sensory channels which served him most effectively.

The program device of "doing together," *i.e.*, participation in performing basic physical exercises, was a method of insuring almost complete participation.

Guest speakers included a representative from the Federal Security Agency (Social Security Administration), the New York City Board of Health, and the OPC Dietitian and Physical Therapist. The speakers generally handled the teaching or presentation of the material, while the clinic team assisted the group members to make the most effective use of the educational method.

Effective presentation of information about ways to protect health resulted in cooperation and rapid and steady learning by the group, particularly when the material presented was simplified and easily digested. The group was taught to take the following measures to safeguard physical health:

1. Learn techniques to prevent accidents in and outside the home.
2. Learn how to reduce the incidence of the common cold.
3. Seek medical advice on the treatment of upper respiratory infections.
4. Learn about the care of the skin and feet.
5. Learn about degenerative diseases in order to prevent (by seeking medical care early) serious complications.
6. Learn when, and when not to use proprietary drugs.
7. Learn the basic rules of nutrition and the importance of special diets in advanced years.

8. Understand the warning signs of possible malignant tumors.
9. Learn about the control and regulation of excretory functions.
10. Understand the roles of tobacco and alcohol in the development of exacerbations of organic diseases.

IMPRESSION

The group meetings were terminated after approximately 20 sessions, or when it was decided by both leadership and membership that all the areas were adequately covered. Many of those attending were helped to become members of ongoing special interest groups in local community health and welfare agencies. The following questions were constantly raised: Have the efforts accomplished their aims? Was there adequate response to the most common complaints? Have the physically and emotionally disabled members of the groups been helped?

The changes which occur are intangible, and do not lend themselves to statistical reporting. However physical examinations and careful observation revealed some indications that the educational program did add years to some lives and often reduced the incidence of chronic suffering.

Group members responded well to the interest taken in them. There was consistently high attendance at meetings, despite occasional adverse weather conditions. From a periodic review of medical records, a greater readiness to make more constructive use of health and welfare services was noted in many instances. Membership in the program was effective in inducing some of the patients, who otherwise might hesitate to ask for medical care, to apply for treatment. The members, as a group, became more health-conscious. The OPC internist noted definite changes in the health picture of several patients, which he attributed to changes in their attitude toward their chronic ailments. Many patients exhibited lessened preoccupation with themselves and with disabling illness. Objective changes were conveyed by the observation that the patients had a brighter outlook about the future and more assurance about themselves. There was a moving away from egocentric tendencies and a more appropriate evaluation of their own assets and limitations.

CONCLUSIONS

A comprehensive team approach to the special problems of the aging, conducted in a group setting, should include some means to reduce medical and social inadequacies. There is also need to compensate for inadequacies that are not reducible, through educating the patient to recognize the potential and current hazards of old age, and to help him evaluate his true assets and meet crisis situations with as little strain as possible.

An over-all goal would be the realization of man's inherent desire to live life to its fullest, not just to exist. Often this goal is limited to the attempt to preserve and utilize what one has as long as possible. Man requires, in order to live, the exercise of his mental and physical constitution. As the individual mem-

ber begins to understand the purpose of the group program, he "takes stock" and assumes more responsibility for his own welfare.

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RELATIONSHIP OF THE TWO-HOUR BLOOD GLUCOSE LEVEL TO TWO ORAL ROENTGENOGRAPHIC FINDINGS*

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INTRODUCTION

A survey of the literature shows that many investigators tend to associate the roentgenographic findings of alveolar bone loss and periodontal widening with diabetes. There is an implication of a linear relationship between these roentgenographic findings and the diabetic state—the more pronounced the diabetes (blood glucose level) the more severe the alveolar bone loss and periodontal widening.

In a previous study (1) we analyzed the relation between oral roentgenographic findings and the *glucose tolerance pattern*. The evidence indicated that there is a *linear* relationship between the glucose tolerance pattern and the presence of alveolar bone loss and periodontal widening. In another study (2) we analyzed the relation between oral roentgenographic findings and *fasting* blood glucose levels. The results pointed to a *parabolic* relationship between the fasting blood glucose levels and the presence of alveolar bone loss and periodontal widening. Thus the total evidence suggested that both hyperglycemia and hypoglycemia are associated with alveolar bone loss and periodontal widening.

This report will analyze the relationship of the two roentgenographic signs (alveolar bone loss and periodontal widening) to the *two-hour* blood *true*-glucose level in a group of 100 routine dental patients. The two-hour concentration was selected because of the general belief that it is more representative of glucose metabolism than is the fasting blood glucose concentration.

REVIEW OF THE LITERATURE

Published material is available regarding the relationship between diabetes mellitus and: 1) alveolar bone loss, and 2) periodontal widening.

Alveolar bone loss. There are several reports on the association of this finding with the diabetic picture (3–9). One investigator (10) observed bone loss in 1 out of every 2 of a group of diabetic children. On the other hand, two teams (11, 12) found no alveolar bone loss. Sheridan *et al.* (13) observed normal alveolar bone in 24 per cent of patients with normal glucose tolerance patterns. They

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TABLE 1

Age Distribution

Age Group	No. of Patients
0–9	1
10–19	9
20–29	19
30–39	27
40–49	19
50–59	17
60–69	8
Total	100

further observed that patients with either increased or decreased glucose tolerance showed a greater incidence of alveolar bone loss and that most of the diabetic patients exhibited considerable bone loss in contrast to other groups of patients having more physiologic glucose tolerance patterns.

Periodontal widening. Rutledge (10) observed this widening in 14 of 20 juvenile diabetics. The findings of Rudy and Cohen (12) are in agreement with those of Rutledge. However, Ziskin *et al.* (14) could not demonstrate periodontal widening in their series of cases. Sheridan *et al.* (13) reported that, in patients with decreased glucose tolerance patterns (persons who would commonly be called diabetic), there was a 62 per cent incidence of periodontal widening. These investigators also observed that the incidence decreased with an increase in sugar tolerance.

CLINICAL MATERIAL AND METHODS

One hundred dental patients were studied in the Section on Oral Medicine at the University of Alabama School of Dentistry. As far as possible, the subjects were drawn at random. Table 1 shows the age distribution—almost a typical unimodal curve. There were 22 males and 78 females.

The roentgenograms on each patient were studied for possible alveolar bone loss and periodontal widening. Alveolar bone loss was rated on a 7-point scoring system in which zero was the score for a normal septal crest; a score of 1 was assigned for minimal alveolar bone loss; 2, for minimal to moderate alveolar bone loss; 3, when half the alveolar support was missing; 4, for moderate to severe alveolar bone loss; 5, for no alveolar support; and 6 for edentulous patients. Periodontal widening was scored on a 4-point scoring system in which zero was the score for no marginal widening; a score of 1 was given for minimal marginal widening; 2, for severe marginal widening; and 3 for edentulous patients.

A true-glucose tolerance test was performed on each patient according to the methods of Somogyi (15, 16) and Nelson (17). No preparatory diet was recommended except for complete fasting for twelve hours prior to the laboratory examination. Complete details regarding the method of investigation are available in the publication by Sheridan *et al.* (13). For this study, only the information derived from the *two-hour* blood glucose determination was utilized.

RESULTS

The two-hour blood glucose levels were considered in relation to: 1) each roentgenographic sign, singly, and 2) a combination of the two signs.

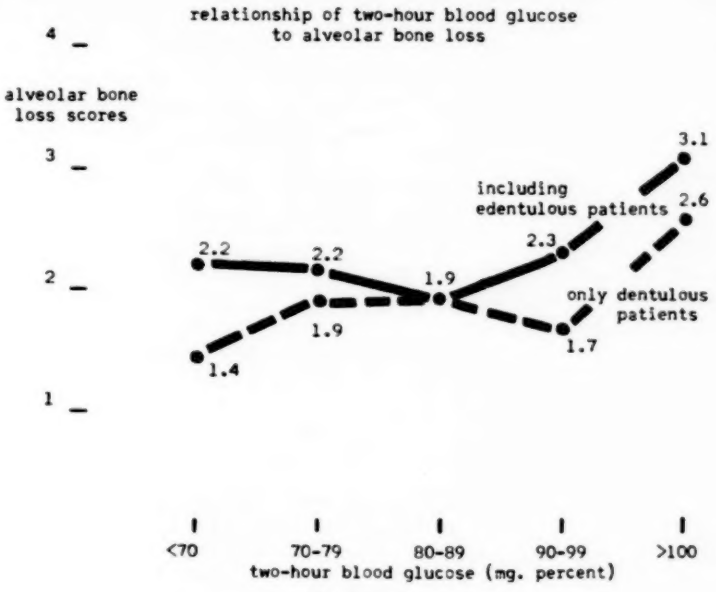

FIGURE 1

Single Signs

Alveolar bone loss

This roentgenographic sign was assessed in terms of: 1) mean scores, 2) coefficients of variation, and 3) statistical significance.

The scores for edentulous patients were included in this analysis since this condition would be an end-result of alveolar bone loss. Although loss of teeth can be due to other causes, the exclusion of these cases would be too discriminatory against those in which tooth loss was due to alveolar bone loss. The available data do not permit the selection of cases in which loss of teeth was accompanied by severe alveolar bone loss.

Mean scores. Examination of Figure 1 shows that alveolar bone loss was least in the patients with a two-hour blood glucose level of 80–89 mg. per 100 ml. The bone loss scores increased at the blood glucose levels of <70, 70–79, and 90–99 mg. per 100 ml., and there was a marked increase at the level of >100 mg. per 100 ml. Figure 1 also shows a comparison with the mean scores obtained on dentulous cases alone. The plotted mean scores for these cases graphically illustrate how these values can be affected by the exclusion of patients who have lost all of their teeth. *It is noteworthy that of the 11 edentulous patients in this study not one had a two-hour blood glucose level in the range of 80–89 mg. per 100 ml.*

Coefficients of variation. Examination of Table 2 reveals that the lowest coefficients of variation were observed at blood glucose levels of 80–89 and >100 mg. per 100 ml. Thus, in these groups the individual values seemed to cluster about the mean more than in the other blood glucose groups.

Statistical significance. From Table 2 it can be seen that there was no statistically significant difference between any of the blood glucose groups when

TABLE 2

Relationship of Two-Hour Blood Glucose Level to Alveolar Bone Loss

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Mean alveolar bone loss score	2.2	2.2	1.9	2.3	3.1
Standard deviation	2.1	1.7	1.1	1.9	1.7
Coefficient of variation	95	77	58	83	55
Mean difference	0.0	0.3	0.4	0.8	
Standard error of difference	.61	.47	.78	.78	
Observed t value	.000	.638	.512	1.025	
Degrees of freedom	37	33	20	43	
P	.5	.5	.5	>.2	

compared to similar groups with levels higher or lower by 10 mg. per 100 ml. This is shown by the probability values of .5 and >.2. The P value was also checked for all the groups. There were no statistically significant differences except when the 80–89 and >100 mg. per 100 ml. groups were compared. This is shown by a P value of <.005.

Periodontal widening

This roentgenographic sign was also assessed in terms of: 1) mean scores, 2) coefficients of variation, and 3) statistical significance.

Mean scores. Figure 2 shows the mean scores for all patients (dentulous and edentulous) and the mean scores when edentulous patients were excluded.

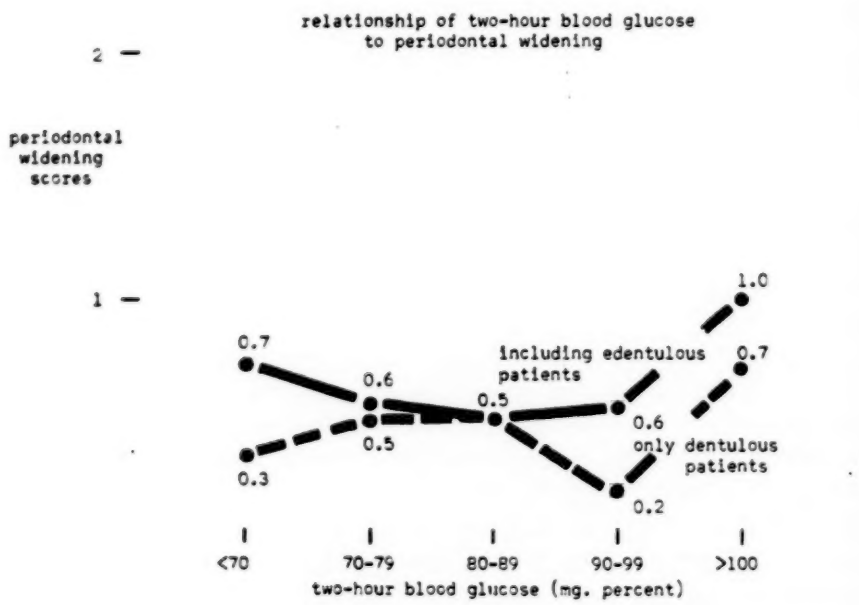

FIGURE 2

TABLE 3

Relationship of Two-Hour Blood Glucose Level to Periodontal Widening

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Mean periodontal widening score	0.7	0.6	0.5	0.6	1.0
Standard deviation	1.1	0.8	0.6	1.1	1.0
Coefficient of variation	157	133	120	183	100
Mean difference	0.1	0.1	0.1	0.4	
Standard error of difference	0.30	0.22	0.45	0.45	
Observed t value	.333	.454	.222	.888	
Degrees of freedom	37	33	20	43	
P	.5	.5	.5	>.2	

Examination of these values shows the effect of excluding the edentulous cases. Patients with severe periodontal widening leading to edentulousness would not be counted if only dentulous cases were considered. This effect was greatest in the <70 and the 90–99 mg. per 100 ml. blood glucose groups. The rest of this analysis pertains to the scores obtained from the study of all the patients. Figure 2 shows that periodontal widening was least in the group with blood glucose levels of 80–89 mg. per 100 ml., and that the incidence of this condition increased as the two-hour blood glucose level rose above or fell below this small range.

Coefficients of variation. From Table 3 it may be seen that the lowest coefficients of variation were shown by the groups with blood glucose levels of 80–89 and >100 mg. per 100 ml. That is, the individual scores were clustered more closely about the mean in these two groups.

Statistical significance. From Table 3 it is evident that there were no statistically significant differences between any of the blood glucose groups when compared to similar groups with levels higher or lower by 10 mg. per 100 ml. This is shown by probability values that are greater than .05. The P value was also checked for all the groups. There were no statistically significant differences shown except when the 80–89 and >100 groups were compared. A P value of <.05 so derived is statistically significant.

Combination of the Two Signs

An analysis of the data was made for alveolar bone loss and periodontal widening. The combination of these two signs was assessed in terms of: 1) mean scores, 2) coefficients of variation, and 3) statistical significance. There was a difference in the scoring systems for these two signs, alveolar bone loss being measured on a 7-point scale, and periodontal widening on a 4-point scale. In order to equate these scores, the periodontal scores were doubled, so that a value could be placed on the combination of these two roentgenographic signs.

Mean scores. It appears from Figure 3 that the relationship between the two-

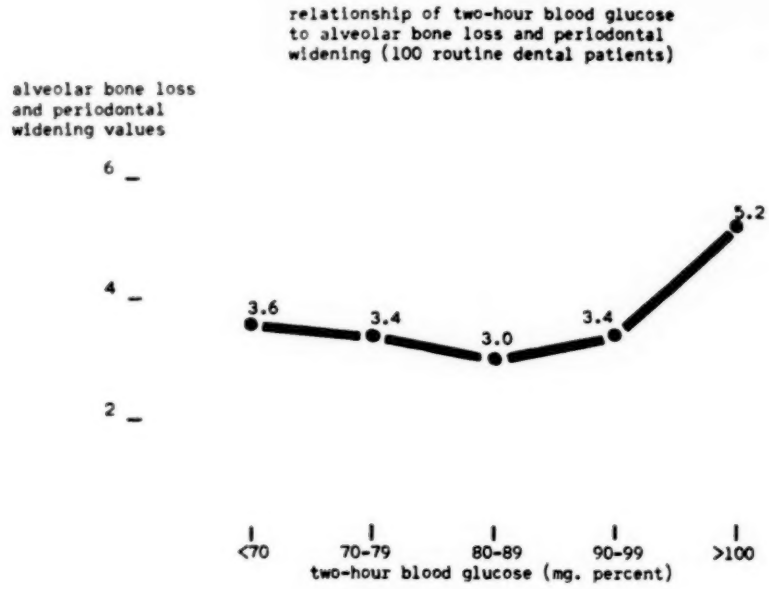

FIGURE 3

hour blood glucose level and the presence of these two signs is parabolic. Thus alveolar bone loss and periodontal widening were least when the two-hour blood levels were in the range of 80–89 mg. per 100 ml. As the two-hour blood glucose level increased or decreased, the frequency of alveolar bone loss combined with periodontal widening increased.

Coefficients of variation. Table 4 shows that the lowest coefficients of variation occurred in the groups with blood glucose levels of 80–89 and >100 mg. per 100 ml. This indicates that the individual scores clustered more closely around the mean in these two blood glucose groups.

Statistical significance. As seen in Table 4, there were no statistically significant

TABLE 4

Relationship of Two-Hour Blood Glucose Level to Both Alveolar Bone Loss and Periodontal Widening

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Mean alveolar bone loss and periodontal widening values	3.6	3.4	3.0	3.4	5.2
Standard deviation	4.3	2.8	2.2	4.1	3.5
Coefficient of variation	119	82	73	121	67
Mean difference	0.2	0.4	0.4	1.8	
Standard error of difference	1.2	0.8	1.7	1.7	
Observed t value	.166	.500	.235	1.058	
Degrees of freedom	37	33	20	43	
P	.5	.5	.5	>.2	

differences between any of the two-hour blood glucose groups and their adjacent groups. A comparison of each group with all others showed no statistically significant differences except between the >100 mg. group and the 70–79 and 80–89 mg. groups. The P values here were <.05 and <.01 respectively.

DISCUSSION

The data will be discussed under the following headings: 1) mean scores, 2) coefficients of variation, and 3) statistical probability values. Because of the close correlation between age and glucose levels, and between age and roentgenographic signs, the age factor will be analyzed in terms of blood glucose concentration and roentgenographic signs.

Mean scores

An analysis of the mean scores for the 2 oral roentgenographic signs, both independently and in combination, point up the fact that the patterns are parabolic. The data indicate that the range of blood glucose normality associated with the lowest incidence of one or both of these particular roentgenographic signs (Table 5) was in the general range of 80–89 mg. per 100 ml. Moreover, two-hour blood glucose levels above and below this narrow range were apt to be associated with a high incidence of abnormal roentgenographic findings.

Coefficients of variation

Generally speaking, the lower the coefficient of variation, the more the individual scores cluster about the mean. Thus, a coefficient of variation of zero is the ultimate, in that it signifies that all subjects provide scores exactly like the mean score.

In Table 6 are summarized the coefficients of variation with respect to the two-hour blood glucose groups and the single and combined oral roentgenographic signs. It can be seen that the individual scores always clustered more closely about the mean in the groups with blood glucose levels of 80–89 and >100 mg. per 100 ml.

Significant probability factors

Table 7 contains a tabulation of the significant probability findings for the single and combined oral roentgenographic signs. It is noteworthy that patients

TABLE 5

Comparison of Mean Scores

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Alveolar bone loss	2.2	2.2	*1.9*	2.3	3.1
Periodontal widening	0.7	0.6	*0.5*	0.6	1.0
Alveolar bone loss and periodontal widening	3.6	3.4	*3.0*	3.4	5.2

TABLE 6

Comparison of Coefficients of Variation

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Alveolar bone loss	95	77	58	83	55
Periodontal widening	157	133	120	183	100
Alveolar bone loss and periodontal widening	119	82	73	121	67

TABLE 7

Comparison of Significant Probability Values

	Relationship of Two-Hour Blood Glucose Levels (mg./100 ml.)	P Value
Alveolar bone loss	80–89 with >100	<.005
Periodontal widening	80–89 with >100	<.050
Combination of alveolar bone loss and periodontal widening	70–79 with >100	<.050
	80–89 with >100	<.010

TABLE 8

Percentage Frequency of Patients with Oral Roentgenographic Signs, by Age Groups

Age Group	Alveolar Bone Loss	Periodontal Widening	Alveolar Bone Loss and Periodontal Widening
0–9	0	0	0
10–19	44	22	11
20–29	78	39	39
30–39	96	52	52
40–49	100	74	74
50–59	100	50	50
60–69	100	86	86

with two-hour blood glucose levels of >100 mg. per 100 ml. showed significant differences in the amount of alveolar bone loss and periodontal widening when compared to patients with glucose levels of 80–89 mg. per 100 ml. The significant difference between these blood glucose groups was maintained when the data for both roentgenographic signs were combined. Moreover, a significant difference was also shown between the 70–79 and >100 mg. groups for the combination of alveolar bone loss and periodontal widening. It is of interest that the two-hour blood glucose groups (80–89 and >100 mg. per 100 ml.) that consistently showed significant differences also demonstrated the lowest coefficients of variation.

Age factor

Some investigators contend that with increasing age the values for normal blood glucose concentration increase. Certainly, the data from which this study is

derived indicate that oral roentgenographic signs occur predominantly in the older age groups (Table 8). Hence, it was thought necessary to analyze the relationship between roentgenographic signs and blood glucose levels in a single age group.

Figure 4 pictorially demonstrates the relationship of two-hour blood glucose concentration to alveolar bone loss and periodontal widening in the 19 patients between the ages of 40 and 49. Examination of Figure 4 and a comparison of these data with those in Figure 3 indicate that the parabola is more exaggerated when the age factor is eliminated. A comparison of Tables 4 and 9 shows that the

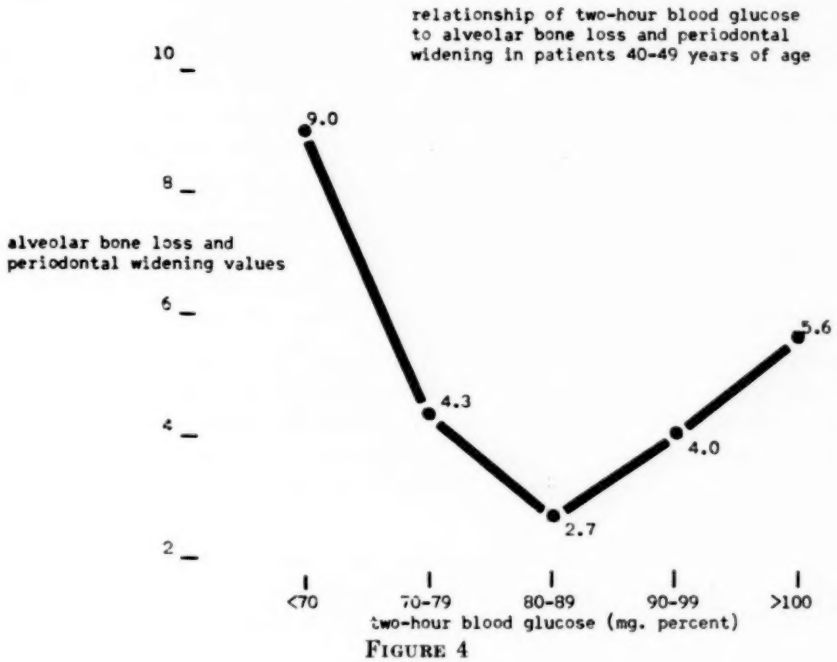

FIGURE 4

TABLE 9

Relationship of Two-Hour Blood Glucose Level to Alveolar Bone Loss and Periodontal Widening in the 40–49 Year Age Group

	Blood Glucose Concentration (mg./100 ml.)				
	<70	70–79	80–89	90–99	>100
Mean alveolar bone loss and periodontal widening values	9.0	4.3	2.7	4.0	5.6
Standard deviation	4.2	0.6	1.5	1.4	2.7
Coefficient of variation	47	14	56	35	48
Mean difference	4.7	1.6	1.3	1.6	
Standard error of difference	3.02	0.98	1.35	1.35	
Observed *t* value	1.556	1.632	0.960	1.185	
Degrees of freedom	3	4	3	9	
P	>.2	>.1	>.4	>.2	

individual scores for this one age group clustered more about the mean than did the scores for the entire group as judged by the coefficients of variation. There were no significant differences when each group was compared to any other, except between the 80–89 mg. and >100 mg. blood glucose groups; here the P value was <.05. It is noteworthy that, although these blood glucose groups still showed a significant difference, there was some loss in the P value (from <.05 to <.01). It thus appears that age or some factor operating with age may be involved in the relationship of the two oral roentgenographic signs and glucose metabolism. However, this factor is not the only, or even the dominant one.

SUMMARY

An analysis is presented of the relationship between two oral roentgenographic signs (alveolar bone loss and periodontal widening) and the *two-hour* blood *true*-glucose level in 100 routine dental patients.

Comparison of the mean score values for the two roentgenographic signs, independently and when combined, demonstrated that the patterns are generally parabolic.

The coefficients of variation showed that, in general, the individual scores clustered more closely about the mean in the groups with blood glucose levels of 80–89 and >100 mg. per 100 ml.

The significant probability values demonstrated a significant difference between the 80–89 and >100 mg. two-hour blood glucose groups for both of the oral roentgenographic signs, singly and in combination.

The findings suggest that the two roentgenographic signs (alveolar bone loss and periodontal widening) are associated with both hyperglycemia and hypoglycemia.

An age factor or some factor operating with age seems to be associated with hyperglycemia and hypoglycemia in the relationship between the two roentgenographic signs and glucose metabolism. However, this factor does not play the only, or the dominant role in the relationship.

It is concluded that the range of normality for the *two-hour* blood glucose level with respect to these two roentgenographic signs is more narrow than usually accepted.

The *fasting* blood glucose level (previously reported), rather than the *two-hour* level, is more representative of glucose metabolism in relation to alveolar bone loss and periodontal widening.

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HOST-TUMOR ANTAGONISM. XVIII. EXPERIMENTAL TREATMENT OF BREAST CANCER IN DOGS WITH AN HYDROLYSATE OF CERTAIN PLANT SEEDS (ONCOLYSIN)*

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INTRODUCTION

The results of a current study we are conducting on the experimental treatment of spontaneous breast cancer in dogs with certain plant seed extracts have shown such promise that it seemed worth while to examine the background of this form of therapy. The plant kingdom is the source of some of our most useful and potent medicines. A number of compounds occurring naturally in fungi and other plants have proved successful in the treatment of some bacterial diseases. The use of plant substances in tumor therapy is not particularly new; undoubtedly it has been going on for centuries.

The material used in this study stems from the work of Dr. S. P. Beebe (1), who in 1914 investigated the claims of an Austrian biologist and chemist, Dr. Alexander Horowitz. Horowitz made an extract of 12 plants and used the mixture as a poultice applied to the surface of tumors, and also as a capsule administered by mouth.

PLANT COMPOUNDS IN THE TREATMENT OF TUMORS

There are many compounds capable of damaging malignant growths, but they are so toxic to normal tissues that they are of little clinical utility. The ideal therapy must selectively damage malignant cells.

Since the differences in biochemistry between tumor cells and normal cells have been shown to be quantitative rather than qualitative, a completely selective chemical is a remote possibility. Because of these factors, the investigation of natural substances may prove fruitful.

Some of our most remarkable drugs are extracted from plants, and several of them have been in use for centuries. Morphine is extracted from the juice of the Indian poppy, quinine from the bark of the cinchona tree, digitalis from the leaves of the purple foxglove, belladonna alkaloids from the leaves and roots of the deadly nightshade, and ephedrine from the roots of the Chinese plant, ma huang.

During the past century, plant extracts have been used for the treatment of animal and human cancers. The relatively recent finding that colchicine, an alkaloid extracted from the autumn crocus, caused regression and cytolysis in tumors revived interest in the use of plant extracts as tumor-damaging agents

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(2). Still more recently it was found that podophyllin, a cathartic extracted from the plant May apple, can produce great damage in experimental tumors (3).

Cotton Mather (4), a New England minister living in the early eighteenth century, and an inveterate scholar of the medicine of the time, made an interesting comment in a letter to the Royal Society of England. In discussing some unique American plants, he mentioned the plant Fagiana, with which an Indian had performed strange cures of cancer.

Mexican herbalists have been treating cancer with certain plants, *e.g.*, Amphyteryngium abstringens and Cola de caballo and others, perhaps for centuries. Arnica, a bark called cancerina, and one called Conteza de cuachalatis have also been used by these Indian herb doctors for the treatment of cancers. The plants are brewed as a tea and taken by mouth. Even though the diagnostic ability of these practitioners regarding internal cancer is very low, their opinions cannot be entirely disregarded.

Extracts of Amphyteryngium abstringens and Cola de caballo have inhibited the growth of tumor implants in D.B.A. mice (5). In the United States Dispensatory (Edition 20, 1918) (6) the following plants are noted as having been used in the treatment of tumors: condurango bark, Echinacea root, poke root, and Solomon's seal (6).

Belkin, Fitzgerald and co-workers (7) systematically tested plant extracts for ability to damage experimental tumors. The plants were grouped for convenience on the basis of the pharmacologic action popularly ascribed to each of them, *e.g.*, cathartics, pesticides, diuretics, and a miscellaneous grouping. The test tumor was Sarcoma 37, implanted into the thigh of CAF mice; suspensions of the plant substances were injected into the contralateral thigh. Of the cathartics tested, 15 plants produced at least one preparation that caused histologic damage in the tumor (7a). Of the diuretics tested, 2 plants induced mitotic arrest at the metaphase; one of these was Chimaphila maculata (spotted pipsissewa leaf) (7b). It is of great interest that the use of "pipsessaway tea" for the treatment of human malignant disease was reported by Mossell (8) in 1818. A decoction of the plant was used to treat 2 cases of "cancer"; cures resulted in about one month. Of the pesticides, extracts from the plant Sinaruba amara damaged Sarcoma 37 markedly.

Taylor, McKenna and Burlage (9a) stated that in their original experiments on the effects of plant extracts on tumor tissue, they expected that plants with recognized toxic properties would be most likely to show the desired effects. However, they soon found that nontoxic plants were also the source of tumor-inhibiting substances. For example, they observed that tumor growths could be retarded by cucumber juice and by extracts of a muskmelon (9b). They had just begun to test plant seed extracts, and had noted tumor growth-inhibiting factors in fractions of alfalfa seeds and beet seeds (9b).

AUTOLYSIN (BEEBE)

The work upon which the present study is based was first carried out in 1914–1915. S. P. Beebe (1, 10a) became interested in the work of Alexander Horowitz, an Austrian biologist and chemist who originated the extract and asked Beebe

and Dr. James Ewing to investigate its merits. The extract was made from a dozen plants in varying proportions. It is of more than passing interest that at least 6 of the 12 plants were investigated independently by Taylor and his group within the past few years, and have been found to inhibit tumor growth in their experimental set-up (5, 9).

Originally, the extract was used as a poultice and also as a pill. With this treatment the malignant mass gradually became edematous and softer. Microscopic examination of sections of tissue taken from and about the tumor showed that the lymphatics were engorged with leukocytes. The exudate, which later on was produced in considerable quantities in the treated area, contained large amounts of broken-down cancerous material, serum, and leukocytes of the small and large mononuclear type. There was at the same time an improvement in the general condition of the patient, as manifested by relief of pain, increased appetite and marked abatement of the toxemia or cachexia accompanying the disease.

It is not necessary to describe the complicated method of preparing the extract originally devised by Horowitz, because Beebe himself later simplified it. Beebe noted that the general improvement of the patient was greater than might be expected from the application of a local irritant, and thought that such improvement must be caused by absorption through the skin of substances dissolved or extracted from the agents in the poultice.

Accordingly, an extract called Autolysin by Beebe was administered to animals in an attempt to obtain both local and general effects. At the point of injection into normal tissue, a local reaction was produced—swelling, redness, heat and tenderness—followed by general leukocytosis, some rise in temperature, and occasionally in human subjects, a chill of varying intensity and duration. When the area of injection was examined microscopically, it exhibited all the characteristics of a moderately acute inflammatory reaction with relatively large leukocytic infiltration. When such extracts were injected directly into a transplantable rat sarcoma, a characteristic reaction occurred which was followed by a peculiar necrosis of the tumor cells. When the skin over the tumor prior to injection was ulcerated, the affected area rapidly degenerated and a mass of necrotic tumor tissue was discharged, followed by healing. If the skin was not broken or ulcerated, the reaction following injection produced a marked infiltration of serum and leukocytes, particularly around the borders of the tumor. The tumor itself, was then gradually absorbed, and there was apparent complete restoration of normal cellular conditions. Rats did not seem to be as susceptible as human subjects to the injections of the extract; in order to produce similar results in the rats, it was necessary to give larger doses.

At first Beebe injected the extract into the tumor itself, but later he used subcutaneous injections into the arm. Definite reactive responses occurred in the growth, namely, swelling, a temporary increase in pain followed in a few hours by considerable relief, and in some forms of tumor, softening and a gradual decrease in size.

In the year prior to February 1916, more than 2000 patients were treated with Autolysin. A large percentage of these patients were in a most desperate

condition (10 b). Many of the cancers were so far advanced that no form of treatment could possibly repair the damage and permit the injured tissues to assume normal function. Beebe observed marked differences in effect in different patients; nevertheless, 80 per cent of the inoperable cancer patients were benefited in some degree. Sometimes the benefit was solely the relief of pain and odor. In the group with the most favorable results, the benefit was often so marked that the patients were able to resume their normal activities and in some instances were clinically well. This record is remarkable when one considers that he was dealing with more or less terminal inoperable cases. Beebe appeared restrained in his claims for Autolysin, but stated that he had not previously seen such consistent improvement with other known remedies, especially if regression in the bulk of the neoplastic tissue were taken as the criterion.

One of the complications mentioned by Beebe can actually be considered as due to the effectiveness of the extract. At times the treatment caused such wide destruction of tumor tissue that, when the tumor involved the region of large blood vessels, the breaking-down process was followed by severe and fatal hemorrhage.

The extract was usually injected subcutaneously into the arm. When the extract was injected into a vascular tumor or intravenously into a patient who had been treated previously, an anaphylactic type of reaction sometimes occurred, that Beebe believed was due to a foreign-protein reaction. In his October 1915 article (10a) nearly all the injections were described as being given into the arm, so that untoward reactions were rare.

Beebe spoke of the pain relief induced by injection of Autolysin. In some instances this was so pronounced that opiates could be discontinued. The discharge and the putrid odor of an ulcerating malignant growth were among the first symptoms to be relieved. There was often improvement in the patient's general condition, including improvement in appetite, digestion, sleep, strength, vigor and weight, and a loss of the cachectic appearance. The most encouraging change was the diminution in the size of the tumor mass, which occurred promptly and was accompanied by a change in consistency. Hard epithelioma and carcinoma became softer and less firmly fixed to the surrounding structures. The metastatic lymph glands were usually the first areas to show the effects of therapy; they became softer and more freely movable, and were gradually absorbed. In some instances these glands became infected, and required external drainage. Some of the mammary tumors gradually softened and changed to a fluctuating mass which could be aspirated with a needle. The contents would often be sterile and consist of a yellowish serum containing many leukocytes in suspension with broken-down cancer cells and cell detritus. Changes in size of inaccessible growths were manifested by relief of obstruction, *e.g.*, freedom of swallowing in patients with cancer of the esophagus, or freedom of defecation in patients with cancer of the rectum.

Beebe believed that the particular histologic type of growth bore no relation to the rapidity with which regression would occur, but that such changes were apparently dependent upon individual differences in reaction to the injections.

He also believed that although Autolysin had until then been used only in

far-advanced cases, the treatment had a distinct field of service in operable cases, both prior and subsequent to operation. He thought that this method might prevent recurrences, but none of the cases had been treated long enough to have any evidence on this point (1).

In Beebe's experience, carcinoma of the mouth and pharynx were particularly resistant to treatment with Autolysin. Gastric cancer was also resistant. Carcinoma of the rectum, uterus and breast were much more amenable to treatment.

In some cases, a more or less specific response occurred upon injection of Autolysin into the arm. There was a reaction in the tumor itself—slight heat, an increase in pain, swelling and softening of the growth, and an invasion of leukocytes into the area. In a large number of patients a marked leukocytosis followed the injections, accompanied by a relatively large lymphocytosis. Some of the most striking effects occurred in patients whose total leukocyte count rose to 20,000 or 30,000 with a relative lymphocytosis of 30 to 50 per cent. Occasionally myelocytes appeared in the blood, and occasionally there was marked eosinophilia (1).

In his third paper (February 1916), Beebe (10b) evinced some bitterness at the antagonistic attitude of the medical world. This antagonism occurred in spite of the fact that neither of his previous papers had advocated the method as a cure. He noted that fully 80 per cent of the persons who had cancer at the time of his writing, ultimately died of the disease. These patients were treated as hopeless cases by the profession when they had reached the inoperable stage. Often he was told by responsible physicians that the only kind thing to do with an inoperable cancer patient was to allay his pain and hope for his early demise. Beebe also complained that an editor, to whom he had submitted an article, stated that any chemotherapeutic measure advanced for the relief of inoperable cancer must be met by an uncompromisingly nihilistic attitude on the part of the medical profession. He complained that many physicians came to observe the effects of Autolysin in his practice but were afraid to try it in their own patients because of possible censure by certain prominent persons.

Beebe stressed that the effectiveness of Autolysin therapy could be determined only by studies in human subjects rather than in lower animals, since the reaction to various therapeutic agents is often not the same in animals and humans.

ONCOLYSIN

The following year Beebe and Williams (11) changed the extract to an acid hydrolysate of alfalfa seed, millet seed or alfalfa meal, prepared in a uniform way and standardized according to its nitrogen content. This extract was offered as a form of nonspecific protein therapy and therefore the product was not named.

Our work with this extract in the experimental treatment of spontaneous breast cancer in dogs, would seem to indicate a much more specific effect, so we have named this extract Oncolysin.

The reason why Beebe and Williams (11) substituted the new extract for the

original Autolysin was that the new compound was a standardized extract of one plant seed. With Autolysin, characteristic protein reactions has developed in some patients. Beebe and Williams believed that although some of the constituents in the original mixture were useless, they nevertheless contributed to the reactions. Therefore they tried many different single seeds and found the results with a standardized extract of alfalfa seed, millet seed or alfalfa meal to be the most satisfactory. In our work, there have been no allergic reactions associated with the use of extract of alfalfa seed or millet seed.

Beebe and Williams thought that the beneficial therapeutic effects of their extract were a consequence of the marked blood changes caused by the injections. These were: an increase in the hemoglobin level and red blood cell count; marked improvement in the shape, size and staining qualities of the red cells; a relative reduction in the proportion of polymorphonuclear leukocytes to about 40 or 45 per cent; a marked relative increase in the proportion of large mononuclear leukocytes to as high as 30 or 35 per cent of the total count; and an increase in size and an improvement in the staining qualities of the large mononuclear cells. These blood changes did not occur after only one injection, but after weeks or months of therapy.

Experimental Study

For the preparation of Oncolysin, we used the method recommended by Beebe and Williams (11) in their last article on the subject.

Preparation of extract

A 50-gram portion of the selected seed is placed in a flask with a reflux condenser, and 1000 ml. of distilled water and 40 ml. of 10 per cent hydrochloric acid are added. The mixture is boiled for three hours and the coarser particles are strained out through gauze. The filtrate is concentrated to approximately 200 ml. and the excess of acid is neutralized with a 10 per cent solution of sodium hydroxide. An abundant precipitate of acid albumin forms when the extract is neutral to litmus. It is best to add sufficient sodium hydroxide to obtain a faintly alkaline reaction to litmus; thus a portion of the precipitate will redissolve. This slightly alkaline solution is filtered and the filtrate concentrated to such a point that its nitrogen content is 0.3 per cent as measured by Kjeldahl determination. If the reaction is very faintly alkaline, the solution may be readily sterilized by boiling. This method is used for both alfalfa and millet seeds. For alfalfa meal extract, Beebe found it best to add only 10 ml. of the 10 per cent hydrochloric acid and boil for only half an hour.

Prepared in this manner, the alfalfa seed hydrolysate contained 1.1 per cent nitrogen; it was diluted three-fold to yield approximately a 0.3 per cent nitrogen content. The millet seed hydrolysate contained 0.14 per cent nitrogen. This was more difficult to prepare and foamed during the procedure. Appropriate tests for sterility were made on all the final compounds.

Testing in dogs

The extracts were given by subcutaneous or intramuscular injection to 10 dogs bearing spontaneous cancer of the breast, after a biopsy was made for diagnosis. Experience is not yet sufficient to permit statements regarding dosage. Administration, in all but 1 instance, resulted in marked reduction in the size of the tumor. When sufficient numbers of animals have been treated, microphotographs,

dosage directions and complete results will be reported. There were no allergic reactions. The first injection was usually accompanied by fever, but this did not occur with later injections. The tumor usually became tender several hours after injection of the extract. In 2 dogs, the tumor decreased to a very small size; another biopsy at that time showed no tumor tissue, but only an acute and chronic inflammatory reaction. We were not allowed to remove the remains of the previous tumor because the owners of the dog believed that it would disappear spontaneously.

DISCUSSION

Some explanation seems necessary for our use of animals rather than humans for testing purposes. We would not be allowed to treat cancer in patients while the tumors were still in the "curable" state. Only terminal patients would be allotted for treatment. No physician would judge the value of surgery or radiation solely on its ability to help the terminal patient. Yet the fate of therapeutic agents for cancer may rise or fall only on the basis of the effect in advanced stages of the disease. In a recent issue of the *New York Times* (12) it was announced that researchers from the New York Veterans Administration Hospital and the Sloan-Kettering Institute of the Memorial Center for Cancer have gone to Nairobi, Kenya, and to Kampala, Uganda to treat patients with lymphosarcoma of the head and neck. The most cogent reason for this choice of location was that "very little extensive surgery and virtually no powerful radiation treatment are available."

Much of the energy expended in the treatment of cancer has been used against the tumor itself, but some therapeutic efforts should be directed toward enhancing the reactivity of the host. Even if such an agent were available, it is doubtful whether it would be effective in the advanced stages of cancer. Yet this type of cancer patient is used in evaluating all new therapeutic agents. Black and Speer (13) studied the lymph-node patterns with special stains in patients with cancer and certain other diseases. They found "degenerative patterns" in far-advanced cases, and "hyperimmune patterns" in early cases. To take advantage of natural immunity, we should be allowed to treat early cases, since the efficacy of the tested drug might be linked to immunologic responses. Otherwise, even valuable therapeutic agents may be doomed to failure because of incomplete testing.

SUMMARY

Background data are presented regarding the use of a plant seed hydrolysate for the treatment of cancer in dogs.

Reasons are given why this extract should continue to be evaluated in early cancer in animals rather than in terminal cancer in human subjects.

Acknowledgment

Dr. Norman Molomut, director of the Waldemar Medical Research Foundation, Port Washington, Long Island, made the alfalfa seed and millet seed hydrolysates for us, according to specifications.

Mrs. H. C. Nauts of the New York Cancer Research Institute first mentioned Dr. Beebe's work to us.

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AN EVALUATION OF COMBINED BENZTHIAZIDE AND RESCINNAMINE THERAPY IN ARTERIAL HYPERTENSION

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During recent years the chemotherapeutic approach to the treatment of essential hypertension has been based predominantly on the use of three main groups of compounds: ganglionic-blocking agents, rauwolfia alkaloids, and sulfonamide saluretics.

Progress in the more immediate past has been particularly notable in the development of new and improved saluretics of the sulfonamide series. This advance was initiated primarily by the discovery that sulfanilamide is an inhibitor of carbonic anhydrase, an enzyme occurring in high concentration in the kidney (1). Carbonic anhydrase is a zinc-containing enzyme which accelerates the conversion of water and carbon dioxide to carbonic acid. In the kidney, carbonic acid in turn dissociates into bicarbonate and hydrogen ions. The hydrogen ions so formed take the place of sodium ions in the glomerular filtrate, thus freeing the latter for reabsorption. When a carbonic anhydrase inhibitor, such as sulfanilamide, antagonizes the action of the enzyme, fewer hydrogen ions become available for exchange and thus fewer sodium ions are released for reabsorption. Filtered bicarbonate ion, no longer forming carbonic acid in the lumen, is also excreted and changes the reaction of the urine from acid to alkaline. The reduction in degree of hydrogen ion formation also causes increased excretion of potassium. This is explained on the basis that hydrogen ions and potassium ions compete in the tubule for excretion, and a reduction in the former automatically permits greater excretion of the latter.

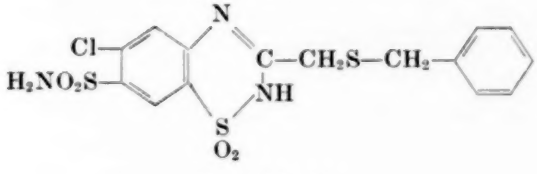
First to be introduced of the sulfonamide saluretics based on this novel mechanism of action was acetazolamide, a compound with much greater capacity than sulfanilamide for inhibiting carbonic anhydrase (2). A relatively brief clinical experience with this agent, however, was sufficient to demonstrate that carbonic anhydrase inhibition as a mechanism to induce saluresis had certain inherent drawbacks. Primarily the depletion of bicarbonate led rather rapidly to a state of metabolic acidosis which automatically resulted in refractoriness to the saluretic action of the drug. Hence, when used clinically, acetazolamide had to be administered on an intermittent basis, with rest periods every few days. Furthermore, the loss of potassium occasioned by this agent proved to be of undesirably high degree, often resulting in symptoms of hypokaliemia.

The subsequent introduction of chlorothiazide (3) overcame these drawbacks to a large extent. Although chlorothiazide is a mild inhibitor of carbonic anhydrase, the induced pattern of electrolyte excretion comes closer to that induced by the mercurials, in that sodium loss is high while potassium and bicarbonate loss is seldom of a degree sufficient to constitute any significant clinical problem

(4). Since bicarbonate is not lost in great quantity, acidosis with resultant refractoriness is seldom seen. Predominantly on the basis of these effects, it is widely postulated that chlorothiazide acts primarily and directly on the reabsorptive mechanism of the renal tubules and only secondarily through carbonic anhydrase inhibition.

The introduction of chlorothiazide was followed rapidly by the development of hydrochlorothiazide. The new compound has a saluretic potency ten or more times that of the parent compound, but there does not appear to be any significant difference in its mode of action or effect on the pattern of electrolyte excretion.

Naturally, with chlorothiazide and hydrochlorothiazide as prototypes, research workers have sought vigorously for new agents which would even more selectively enhance sodium excretion without interference with potassium or bicarbonate excretion. In pursuit of such study, P'An and associates (5) observed that the introduction of a benzthiomethyl group into position 3 of the heterocyclic ring brought about a pronounced increase in diuretic potency. This discovery led to the synthesis of the compound, benzthiazide (Naclex®).[1] The chemical constitution is 3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4-benzathiadiazine-1-1-dioxide, according to the formula:



Benzthiazide

Although under certain experimental conditions it is a more powerful carbonic anhydrase inhibitor *in vitro* than chlorothiazide, the induced pattern of electrolyte excretion in the dog and the rat more closely resembles that induced by chlorothiazide than by the classic anhydrase inhibitor, acetazolamide. This suggests that its saluretic effect is primarily based on a mechanism other than carbonic anhydrase inhibition (5). In the dog and rat it proved to be four and eight times respectively more potent than chlorothiazide in increasing urine flow, and seven and sixteen times respectively more potent in enhancing the excretion of sodium and chloride.

The action of benzthiazide in the human subject has been reported by Ford (6). By careful assay, Ford demonstrated that benzthiazide exercised a natriuretic effect four times greater than its kaliuretic effect. Furthermore, bicarbonate excretion was enhanced only slightly, and there were no significant alterations in serum electrolyte levels following repeated administration. In various states of edema it provided effective saluretic action, and in a limited group of hypertensive patients it yielded impressive results. In 5 patients not receiving antihypertensive therapy, benzthiazide caused a fall in mean blood pressure (diastolic pressure plus one third the pulse pressure) from an average of

[1] Generously provided by A. H. Robins Co., Inc., Richmond, Va.

141 to an average of 117 mm. Hg. The addition of benzthiazide to the regimen also produced a further substantial fall in pressure in patients already receiving rauwolfia, either alone or in conjunction with mecamylamine in ganglionic-blocking doses. The antihypertensive effect of the drug was also demonstrated by its ability to replace hydrochlorothiazide in an antihypertensive regimen without causing alteration in blood pressure readings.

For purposes of general practice, particularly in the management of elderly patients with arterial hypertension, the author has always preferred to employ sulfonamide saluretics in conjunction with rauwolfia rather than with ganglionic-blocking agents. This preference is based on the tranquilizing effects of rauwolfia, a drug which seems to be of benefit in controlling the tendency to agitation and excitement in hypertensive patients, as well as being potentially less toxic than the ganglion-blockers. Recent reports on rescinnamine (Moderil®),[2] a rauwolfia alkaloid identified as the trimethoxy-cinnamic ester of methyl reserpate, have indicated that it is effective in hypertension (7–9), and that it is somewhat better tolerated than reserpine (7, 8).

Since the combination of benzthiazide and rescinnamine appeared to the author to hold promise of effectiveness in the management of hypertension, a clinical trial was conducted in a representative group of patients.

CLINICAL MATERIAL AND METHODS

Subjects

Sixty hypertensive patients were studied. They were drawn in part from a middle-class general practice in an urban area and in part from the inmates of a well-organized nursing home predominantly devoted to the care of geriatric patients. The two sexes were represented in approximately equal proportions, and the patients ranged in age from 60 to 85 years.

Method of study

The subjects were divided into three groups.

Group I consisted of 25 ambulatory patients suffering from Class I–III (American Heart Association classification) hypertensive disease. All previous antihypertensive medication was discontinued for at least two weeks prior to study in order to permit blood-pressure levels to revert to "untreated" values. Thereafter treatment was instituted according to the following scheme:

first and second weeks:	rescinnamine, 0.25 mg. three times daily.
third and fourth weeks:	rescinnamine, 0.25 mg. three times daily, plus benzthiazide, 50 mg. three times daily.
fifth and sixth weeks:	same dosage of both drugs twice daily.
seventh and eighth weeks:	same dosage of both drugs once daily.

Group II was comparable to Group I in consisting of 25 ambulatory patients with Class I-III hypertensive disease. After a two-week "no treatment" period, therapy was carried out in the same manner and dosage as in Group I, with the exception that the period of therapy with rescinnamine alone was omitted.

Group III consisted of 10 hospitalized geriatric patients ranging in age from 60 to 84, suffering from Class II-IV hypertensive disease. After a similar two-week rest period,

[2] Generously provided by Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

treatment followed the schedule outlined for Group I, with the exception that therapy was continued at the final dosage level for six weeks to make a total treatment of period of twelve weeks.

The dietary intake of sodium in the patients of Group III was limited to 1.0 Gm. daily, but no attempt was made to control the intake in the patients of Groups I and II. All groups were given the customary and necessary supportive therapy such as digitalis and vitamin supplements, but care was taken to avoid any additional medication with an intrinsic antihypertensive effect.

Each patient underwent an initial work-up consisting of a complete history, physical examination, funduscopy, urinalysis, blood count, and renal and hepatic evaluation. Thereafter, routine physical examinations were conducted at intervals of five to seven days, and a further complete work-up was carried out at the conclusion of the study. Serum values for sodium, potassium and chloride were determined periodically in the patients of Group III.

RESULTS

Group I

The fall in mean blood pressure in the patients of Group I is shown in Figure 1. By observing the gross gradient changes, it can be seen that rescinnamine (Moderil) alone during the initial two weeks produced only a moderate fall in mean blood pressure (diastolic plus one-third the systolic pressure). The average fall in systolic pressure was 12 mm. and in diastolic pressure, 8 mm. Hg. In sharp contrast, during the third and fourth weeks when benzthiazide (Naclex) was added to the regimen, there was a more pronounced decline; the average systolic and diastolic pressures fell respectively an additional 22 and 16 mm. Hg. In only 4 of the 25 patients in this group was the effect too slight to be considered of clinical significance. All of these 4 patients were suffering from malignant arteriolar nephrosclerosis. In Figure 1 it may also be seen that the reductions in dosage instituted at the beginning of the fourth and sixth weeks did not diminish the antihypertensive effect, so that a maintenance dosage only one-third of that used for initiation appeared to be adequate. With the exception of 4 treatment failures, this dosage of 50 mg. of benzthiazide and 0.25 mg. of rescinnamine once daily appeared to maintain the patient in the "dry" state with no need for booster injections of mercurials.

Group II

In this group, institution of *combined* benzthiazide and rescinnamine therapy promptly produced a marked fall in both systolic and diastolic pressures in the majority of cases. The average fall in blood pressure after two weeks of therapy was 24 mm. systolic and 16 mm. diastolic (Figure 2). Again, the reduction in pressure was well maintained despite the subsequent reduction of dosage. There were only 5 failures in this group—in cases of malignant arteriolar nephrosclerosis considered to be in the irreversible phase. In these 5 cases, albuminuria (4 plus), congestive rales, hepatomegaly and other signs persisted relatively unchanged despite therapy.

In 15 of the 25 cases in this group, placebos were substituted for the active drug at the conclusion of the study. Within three to five days the blood pressure

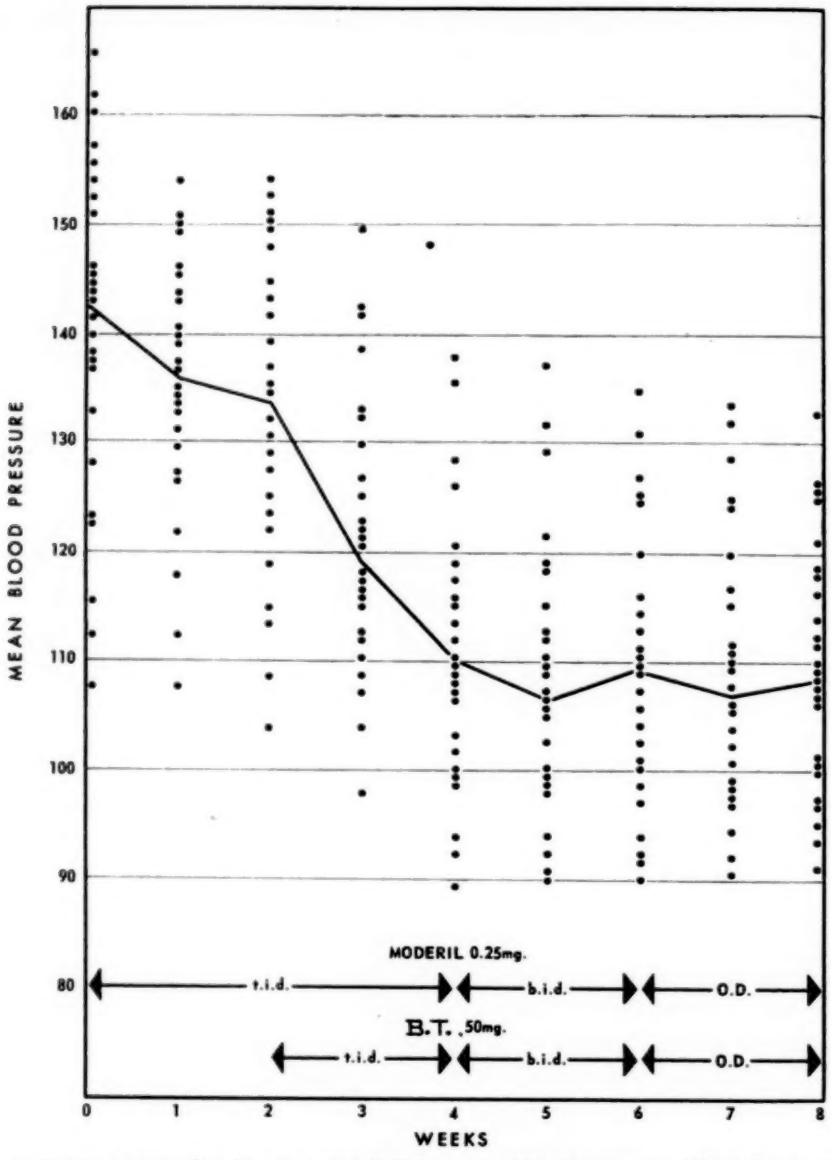


FIG. 1. Scattergram showing average fall in mean blood pressure (diastolic + ⅓ pulse pressure) in 25 patients of Group I treated with rescinnamine (Moderil) for two weeks, then with the addition of benzthiazide (B.T.).

had mounted to pretreatment levels and all the former symptoms had returned. Reinstitution of active therapy brought about prompt symptomatic and objective response in all cases.

Group III

The 10 patients in this group were of more advanced age and in a more advanced stage of the disease than the patients in the other two groups. All cases were classified as chronic hypertensive cardiovascular disease, Class II–IV, and

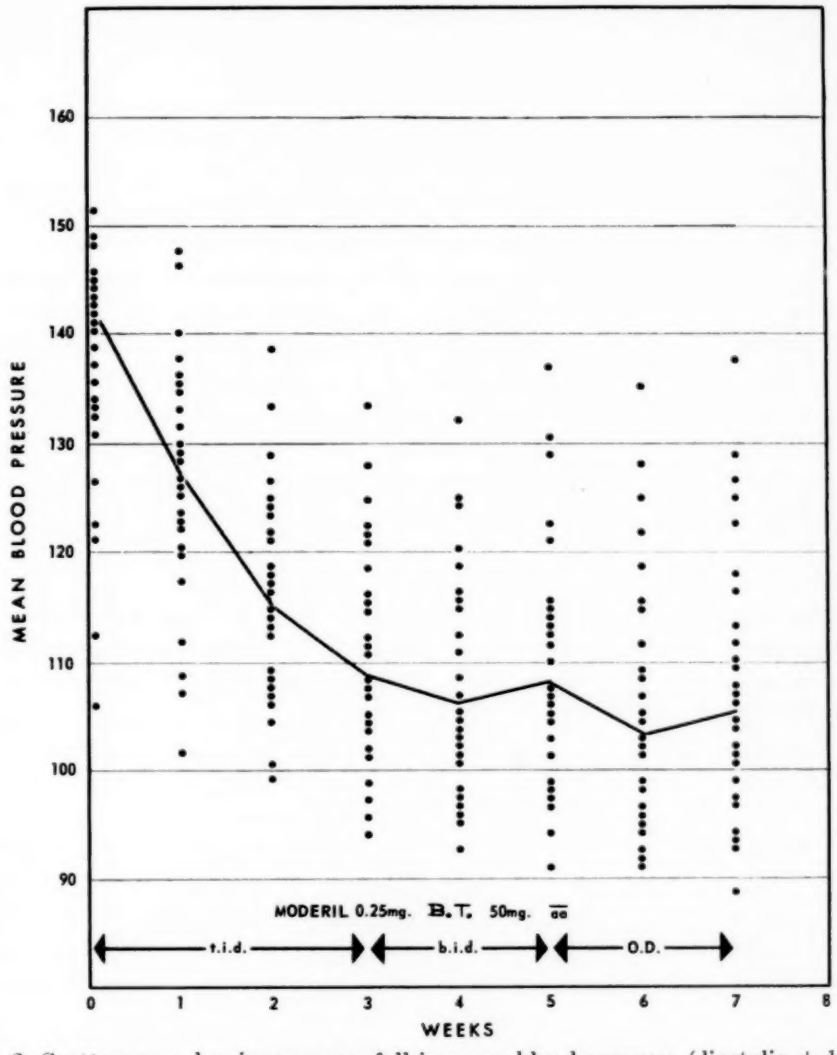


FIG. 2. Scattergram showing average fall in mean blood pressure (diastolic + ⅓ pulse pressure) in 25 patients of Group II treated with a combination of rescinnamine (Moderil) and benzthiazide (B.T.).

all the patients were moderately to severely agitated at the commencement of study. Six of the 10 had previously sustained cerebrovascular accidents and manifested varying degrees of residual neurologic defect. Three had well controlled diabetes and were taking chlorpropamide.

Initial administration of rescinnamine (Moderil) alone in a dosage of 0.25 mg. three times daily for two weeks produced only a moderate hypotensive response. In general, the decrease in systolic pressure ranged from 15–30 mm., and the decrease in diastolic pressure from 10–15 mm. (Table 1). The addition of benzthiazide (Naclex) to the regimen caused an intense diuresis, the loss of fluid being sufficient to account for a weight loss of 2–9 pounds. Blood pressure was further reduced so sharply that in all but 1 patient it reached normotensive levels. In

TABLE 1

Effect of Rescinnamine and Rescinnamine plus Benzthiazide in 10 Patients with Severe Hypertension (Group III)

Patient No.	Blood Pressure (mm. Hg)		
	Prior to treatment	After rescinnamine for only 14 days	After combined rescinnamine and benzthiazide for 10 weeks
1	200/100	160/86	140/80
2	210/96	170/70	150/74
3	170/94	170/80	130/80
4	230/110	190/90	140/80
5	230/120	230/120	150/80
6	220/110	200/90	176/80
7	200/110	200/100	155/80
8	188/92	184/92	150/80
9	210/120	190/100	140/80
10	194/94	182/84	150/80

this remaining patient, the blood pressure had initially been 210/110 mm. Hg, but it became stabilized at 176/80 mm. All effects were well maintained while the frequency of administration was reduced, first to twice daily and then to once daily. Periodic study of serum electrolyte concentration failed to show any significant alteration, and no symptoms of hypopotassemia were detected.

General

In all groups there was a gratifying symptomatic response paralleling the fall in blood pressure. The tranquilizing effects of rescinnamine were particularly notable in the patients of Group III, all of whom had previously manifested some degree of agitation and anxiety, an exacerbation of which had been promptly reflected in an aggravation of the hypertensive symptoms. With rescinnamine therapy, episodes of acute anxiety were almost eliminated and agitation was largely controlled. With the institution of benzthiazide treatment there was usually a distinct increase in urine volume for six to eight days, and in cases characterized by peripheral edema there was disappearance of the edema. Albuminuria frequently cleared, and in cases of hepatomegaly the liver gradually became smaller. Basal rales attributable to pulmonary edema also tended to disappear. Many patients commented favorably also on the relief of symptoms common to hypertension, such as headache, vertigo and palpitation.

No toxic effects were observed during the course of study and none of the laboratory examinations revealed unusual findings attributable to therapy. None of the subjects under study sustained either cerebrovascular accident or coronary thrombosis during the period of observation.

SUMMARY

The antihypertensive effects of rescinnamine (an alkaloid of rauwolfia) and benzthiazide (a new sulfonamide saluretic) have been studied in 60 patients.

Rescinnamine (Moderil) alone usually induced a moderate fall in blood pressure which was further substantially increased by the addition of benzthiazide (Naclex) to the regimen.

The combined therapy, in addition to its antihypertensive effect, caused lessening or disappearance of peripheral edema and produced notable improvement in the symptoms commonly associated with hypertension. The tranquilizing effect of rescinnamine was particularly beneficial in obviating agitation and in preventing exacerbation of hypertension due to episodes of acute anxiety.

Therapy was not accompanied by any clinical signs of toxicity, and laboratory examinations failed to reveal any deleterious influence on organ functions.

On the basis of this experience it is concluded that combined rescinnamine-benzthiazide therapy for arterial hypertension, when conducted with reasonable precautions, is safe and effective. It is of particular value in cases in which an anxiety component is an aggravating factor. Once the full therapeutic response is achieved, the maintenance dosage is usually one tablet of each drug given daily in the morning.

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LETTER TO THE EDITOR

LIPOTROPIC THERAPY FOR PERCEPTIVE (NERVE) DEAFNESS IN THE ELDERLY

To the Editor:

No practical procedure for the treatment of senile perceptive (nerve) deafness is recognized. Yet, as the population of older subjects steadily increases, the condition is seen more frequently. There are reports indicating that lipotropic-oxytropic preparations have been helpful in the treatment of degenerative processes affecting vision in the older age groups. Therefore, it seemed worth while to determine if a product of this type might have value in elderly patients presenting hearing impairments closely associated with the aging process. The product selected for study was Lipotriad.[1] Each half ounce of the liquid contains 1 Gm. of choline, 1 Gm. of inositol, and ¼ Gm. of methionine, plus B and B-complex factors in dietary supplement amounts. It is available also in capsule form, three capsules being the exact equivalent of 1 teaspoon of the liquid.

CLINICAL MATERIAL AND METHODS

Sixty patients with a definite perception deafness were selected for the study of lipotropic therapy of (nerve) deafness in the elderly. Lipotriad was started in a dosage of 1 teaspoon of the liquid, or three capsules, three times daily. It was intended that this therapeutic schedule would be maintained over a prolonged period of time in each case. However, as the study progressed, half of the original patients were removed from further consideration because of their failure to cooperate fully in the treatment program. Thus, data have been obtained on 30 patients treated with the lipotropic preparation for a period of twelve to thirty-six months. In addition to this oral treatment, nicotinic acid and vitamin B_{12} were given intravenously once weekly. The dose of nicotinic acid was dependent upon the patient's reaction and was usually started at about 20 mg. It was gradually increased until the patient experienced definite vasodilatation. This dose may be as high as 300 mg. The dose of vitamin B_{12} remained at 1000 μg. (1.0 ml.).

All patients were examined periodically during the course of study. On the occasion of each office visit, the subject was asked to report his own impressions of the possible benefits he was receiving from the medication. Audiometric examinations were made by the Cincinnati Speech and Hearing Center, on a double-blind basis.

RESULTS

In this study, 10 per cent of the 30 subjects followed for one to two years during treatment with Lipotriad obtained varying degrees of objective relief of hearing loss. This would indicate that only a small percentage of patients may be helped by such a preparation. However, to those subjects who experienced even a small improvement in hearing, the results were impressive. It appears logical, therefore, to suggest that a six-month course of Lipotriad plus nicotinic acid and vitamin B_{12} be tried in patients presenting senile perceptive deafness. Treatment for this length of time should be sufficient to determine whether or not acuity of hearing can be measurably increased through the use of a potent lipotropic preparation.

[1]Manufactured by Smith, Miller and Patch, Inc., New York, N. Y.

In these elderly deaf subjects, subjective responses to treatment should not be glossed over lightly. If improvement in well-being can be obtained through the daily use of a nutritional corrective, careful consideration should be given to the routine administration of such a preparation. It is usually true that older patients do not eat enough food of the right quality.

The general condition and sense of well-being improved in all 30 patients who participated fully in the program. In no instance were significant side-effects observed.

One of the subjects with complicating arthritis stated that after a few months of Lipotriad therapy his internist had noted a marked improvement in his condition. In another patient with choroiditis in one eye, an improvement was noted after three months of continuous therapy; ophthalmoscopic examination showed a partial revacularization of the edges of the affected area.

Several patients expressed the opinion that hearing had improved while taking Lipotriad, but this was not confirmed by audiogram. However, the audiogram findings correlated closely with clinical improvement in 3 other patients who received Lipotriad therapy for periods of one to two years.

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Abstracts of Current Literature

POLYOESTRADIOL PHOSPHATE IN THE TREATMENT OF CARCINOMA OF THE PROSTATE.

Bourque, J. P. *Canad. M.A.J.* **83:** 439 (Aug. 27) 1960.

Sixty-two patients with carcinoma of the prostate were treated as follows: 1) 32 with urinary symptoms and normal acid phosphatase levels received 40 mg. of polyestradiol phosphate (Estradurin) intramuscularly once weekly; 2) 12 with metastatic pain but no radiologic evidence of metastases, and with elevated acid phosphatase levels received two injections weekly; and 3) 18 patients with urinary symptoms, pain from pelvic and spinal metastases, and elevated phosphatase levels in the absence of improvement with an injection once weekly, received the drug daily for three to four weeks and then two injections per week. A palliative operation was performed in 56 of the patients. The treatment period covered three years. Forty-one patients are alive and comfortable. Twenty-one have died. The estrogen therapy reduced the tumor size in 3 patients of the first group so that radical perineal prostatectomy could be performed. The other 38 showed good clinical improvement. The tumor regressed in 22. Pain due to metastases markedly decreased or disappeared. In 1 patient, administration of polyestradiol phosphate accelerated tumor growth and the patient was one of those who died. Polyestradiol phosphate had the advantage of being administered for long periods without noticeable side-effects. Pain from metastases was more effectively relieved than with other estrogens.

THE DEPOSITION OF AGING PIGMENT IN THE HUMAN CEREBRAL CORTEX.

Brody, H. *J. Gerontol.* **15:** 258 (July) 1960.

When pigment is found in the cytoplasm of nerve cells in the cerebral cortex, the greatest amount appears in the cells of the pyramidal, or third, layer. Cells from this layer in 20 brains were examined. No pigment was found in cells from children, newborn to two months of age. Neither did other layers of the cortex in children show lipofuscin material. The number of cells containing pigment increased with age; the majority of the cortical cells in persons aged 79 to 95 years contained pigment. However, in most of the cells pigment was scattered and in only a few was it clumped. The highest percentage of heavily pigmented cells was found in the precentral gyrus, and the lowest percentage was in the striate cortex. The high percentage within the precentral gyrus may be due to the presence of larger-sized pyramidal cells in the third layer. Only a slight decrease was seen in nonpigmented cells in the striate cortex between young adult and middle-aged persons. The decrease was sharper in cells containing scattered and clumped pigment between these age periods.

ELECTROCARDIOGRAPHIC CHANGES SIMULATING MYOCARDIAL ISCHEMIA AND INFARCTION ASSOCIATED WITH SPONTANEOUS INTRACRANIAL HEMORRHAGE.

Cropp, G. J., and Manning, G. W. *Circulation* **22:** 25 (July) 1960.

In 15 of 29 cases of subarachnoid hemorrhage, the electrocardiogram showed abnormalities suggesting recent myocardial infarction. The most prominent features were RS-T segment changes that were ischemic in nature, and T-wave abnormalities most frequently seen in leads I, aV_1, the mid and lateral precordial leads. Of 14 low or negative T_1 patterns, 5 were flat to 0.5 mm. in height, and 9 were negative, the most negative deflection being 3 mm. In 1 instance there was nodal rhythm with right bundle-branch block and progressive changes in postoperative tracings. Increased T-wave amplitude was not prominent in this

study. Two-thirds of the patients with ischemic or infarct-like patterns showed prolonged Q-T intervals. There were no important abnormalities in the P-waves and P-R intervals. The heart rate and rhythm showed no characteristic pattern. The RS-T segment changes and T-wave abnormalities appeared to be directly related to intracranial hemorrhage since they appeared in the presence of normal cardiovascular findings. This assumption was substantiated by 4 postmortem examinations; the site of intracranial bleeding could be located but there was no evidence of myocardial infarction or coronary artery narrowing. The hypothesis is presented that these electrocardiographic abnormalities are caused by lesions in the cerebral cortex of the orbital surface of the frontal lobes (area 13) in the vicinity of the carotid siphons, the anterior communicating artery, and the anterior cerebral arteries. It is important that electrocardiographic changes in patients with spontaneous intracranial hemorrhage not be misinterpreted. In the absence of a history or clinical findings of heart disease, an electrocardiogram showing changes suggestive of recent infarction or acute myocardial ischemia should be interpreted as indicative of intracranial disease rather than heart disease.

SUSTAINED RELEASE PENTYLENETETRAZOL-NICOTINIC ACID THERAPY IN SENILE PATIENTS.

Curran, T. R., and Phelps, D. K. *Am. Pract. & Digest Treat.* **11:** 617 (July) 1960.

Twelve of 23 patients aged 52 to 88 years with manifestations of cerebral arteriosclerosis were greatly improved, and 5 showed a fair degree of improvement when treated for three months with a sustained-release dosage form of pentylenetetrazol with nicotinic acid. One tablet containing 150 mg. of the former with 300 mg. of nicotinic acid was administered in the morning and at night. In addition to atherosclerosis, these patients exhibited other degenerative diseases and more than half had had cardiovascular accidents or disease, or both. The most marked mental improvements were in alertness, memory, mood, emotional stability, orientation and cooperation. Memory and the ability to grasp everyday problems also were improved. The most notable physical improvements were in appetite, sleep patterns, general activity, paresthesias, aphasia, transient cerebral ischemia, and sensorium. Symptoms recurred when a placebo was substituted for the drug but could be overcome by reinstituting therapy. No significant increases in blood pressure occurred, but the diastolic pressure was reduced from 10 to 50 mm. Pulse, rhythm, and electrocardiogram were not affected. Elevated serum cholesterol levels in 3 patients were reduced. Side-effects consisted of flushing in 1 patient and mild nausea in 1 patient which could be controlled by taking the tablets with the morning and evening meals. In 5 of the 6 patients who did not improve, little or no benefit was anticipated because of their advanced state of deterioration or long-established psychoses. The remaining patient not improved had senile heart disease and a dissecting aneurysm of the aorta. The sustained-release form of therapy had the advantages of reducing the frequency of administration, lack of side-effects, maintenance of continuous treatment, and good cooperation from the patient.

TEMPORAL (GIANT-CELL) ARTERITIS ASSOCIATED WITH GANGRENE OF SCALP.

Fleischl, P., and Oldham, B. E. *Brit. M. J.* **2:** 439 (Aug. 6) 1960.

This is the third time a case of gangrene of the scalp has been reported in association with temporal arteritis. Histologic examination of a biopsy specimen of the left temporal artery showed granulomatous lesions with giant cells, extending from the intima into the media. The internal elastic lamina was fragmented. There was evidence of involvement of the ophthalmic and the temporal arteries. Vision in one eye was 6/60. The patient, a man aged 85 years, responded well to 40 mg. of prednisone daily. Severe headache of twelve months' duration disappeared within forty-eight hours. Subsequently the dosage could be reduced to 5 mg. daily given with 10 units of ACTH-gel weekly, freedom from headache being used as the clinical guide.

SELECTIVE INHIBITION OF THE SYMPATHETIC NERVOUS SYSTEM IN MAN WITH BRETYLIUM TOSYLATE, A NEW ANTIHYPERTENSIVE AGENT.

Freis, E. D.; Sugiura, T., and Liptak, D. *Circulation* **22:** 191 (Aug.) 1960.

Bretylium tosylate partially inhibited sympathetic vasoconstrictor reflexes in man at a dose level of 50 mg. intravenously, and completely inhibited the Valsalva "overshoot" in arterial pressure and the digital vasoconstrictor response to a deep breath at a level of 150 mg. At 150 mg., it also inhibited but did not completely block the cold pressor response. Orthostatic hypotension was minimal at 50 mg. but moderate to severe at 100 mg. The intravenous doses required to produce a hypotensive effect in hypertensive patients varied from 50 to 150 mg. Bretylium tosylate was given alone to 8 ambulatory patients with moderate to severe hypertension. In 8 it was substituted for a blocking agent, and adjunctive medication with chlorothiazide or hydrochlorothiazide or hydralazine was continued. The starting dosage was 600 mg. daily, with adjustments according to the response. Administration was continued for one to five months. The effective antihypertensive dosage varied widely, and some patients who had no adjuvant therapy failed to respond to 3000 mg. in a day. Among patients receiving adjunctive therapy, the smallest effective daily dosage was 200 mg., but 1 patient failed to respond to 3000 mg. Without chlorothiazide, most responded to 1800 to 2400 mg.; with chlorothiazide, they responded to 1000 to 1200 mg. Side-effects consisted of orthostatic faintness, tenderness over the parotid glands with pain on mastication, and in a few male patients failure of ejaculation. The heart rate did not change significantly and no arrhythmias occurred. There was some evidence of tolerance, in that patients responded to smaller doses initially than during long-term administration. With continued treatment, narrowing occurred in the spread between blood pressure in the supine and erect positions. Because bretylium tosylate has the property of causing orthostatic faintness and collapse, and there is a wide dosage response range in different patients, individualized and painstaking dosage adjustments are necessary. Therefore, this drug probably will be used to best advantage in severe hypertension not controlled with chlorothiazide alone, or in combination with reserpine or hydralazine.

SERUM PROTEIN-BOUND IODINE CONCENTRATION IN BLOOD OF EUTHYROID MEN AGED 18 TO 94 YEARS.

Gaffney, G. W.; Gregerman, R. I.; Yienst, M. J., and Shock, N. W. *J. Gerontol.* **15:** 234 (July) 1960.

In 192 healthy men, aged 18 to 94 years, protein-bound iodine in blood plasma or serum was estimated by modifications of alkaline ashing or chloric acid methods. The findings of this study and other available evidence do not support the proposition that there is alteration of the level of PBI with increasing age. Sources of variance in the results were investigated by duplicate determinations on specimens, repeated determinations on a pooled specimen, and by repeating the determination one or more times in selected subjects on specimens of blood drawn after an interval of one day to seven months. The data lead to the inference that within individuals the variability due to biologic factors (0.1–1.2 μg./100 ml.) is larger than that due to technical analytical factors (0.3–0.4 μg./100 ml.). An increase in the interval between tests (from an interval of 1–13 days to an interval of 13 days to 7 months) did not increase the standard error of measurement. The mean value for all subjects by the chloric acid method was 6.55 ± 1.2 μg./100 ml., and for the alkaline ashing method 4.97 ± 0.87 and 5.53 ± 0.90 from two different laboratories. (From authors' summary.)

MASSIVE INTESTINAL INFARCTION WITHOUT VASCULAR OCCLUSION ASSOCIATED WITH AORTIC INSUFFICIENCY.

Hoffman, F. G.; Zimmerman, S. L., and Cardwell, E. S., Jr. *New England J. Med.* **263:** 436 (Sept. 1) 1960.

Three cases of massive intestinal infarction without mesenteric vascular occlusion, associated with aortic insufficiency, are reported, together with a review of 2 cases from

the literature. In 1 case, abdominal pain preceded the fatal episode by one month; in the other 3 it was part of the terminal episode. Congestive heart failure was present in 2 of the 5 cases in the series. In 4, the cause of the aortic insufficiency was syphilis. No histologic evidence that this disease contributed in any way to the development of intestinal infarction was found. Massive intestinal infarction without vascular occlusion is an uncommon occurrence. Although attention is called to its association with aortic insufficiency, it may occur rarely with other types of heart disease and in a variety of unrelated conditions. When associated with aortic insufficiency, the infarction was always related to distribution of either the superior or the inferior mesenteric arteries, or both, in sharp contrast to the segmental distribution of this lesion reported in cases not associated with aortic insufficiency. Various mechanisms have been proposed, and are reviewed, in an attempt to explain the pathogenesis of intestinal infarction without occlusion. Of these, the physical basis that involves the law of LaPlace is attractive. The cause of abdominal pain noted with aortic insufficiency cannot be explained unequivocally. Possibly one mechanism, or a combination of mechanisms may be involved. In only 1 patient did pain precede by any significantly long interval the onset of intestinal infarction. (From authors' summary and conclusions.)

APPENDICULAR GRANULOMA.

LaBrun, H. I. *Brit. J. Surg.* **46** (195): 32, 1958; through Excerpta Med. (Gerontol. & Geriatrics) **3:** 101, 1960.

Details are given of 7 instances of an unusual type of appendicitis that is characterised by excessive production of granulation and fibrous tissue and that clinically resembles carcinoma of the cecum. The factors that appear important for production of this condition are: 1) retrocecal position of the appendix with the appendix having no contact with the peritoneum; 2) rupture of an appendicular abscess into the cecum; and 3) age. Five of the patients were past 70 years of age, and 2 were between 55 and 60. At operation the typical finding is a hard mass in the posterior wall of the cecum with fixation to the posterior abdominal wall. Usually the appendix cannot be recognized until the cecum has been mobilized, and even then only the proximal part may be seen. Right hemicolectomy is the recommended treatment, although antibiotic treatment may be tried if operation is contraindicated.

STUDY OF RENAL ISCHAEMIC TUBULAR ATROPHY IN 79 PATIENTS WITH ARTERIAL HYPERTENSION.

Lefebvre, R., and Genest, J. *Canad. M. A. J.* **82:** 1249 (June 18) 1960.

Renal vascular and parenchymal lesions were studied in 71 cases of hypertension in which necropsy was performed, and in 8 patients who underwent unilateral nephrectomy for the relief of hypertension. Sixty-three of the patients in the necropsy series had ischemic tubular atrophy (ITA) characterized by small shrunken but viable tubules lined with small cuboidal epithelial cells, often with clear cytoplasm. The higher grades of ITA were observed in younger patients. With more widespread tubular atrophy, kidney weights were decreased. Kidney function was poor in 24 of 31 cases, whereas good function was present in cases with minimal parenchymal atrophy. Study of intrarenal vessels showed that the degree of vascular sclerosis and narrowing almost paralleled the intensity of ITA. The arcuate, interlobular, and afferent arterioles were most severely affected. The grade of ITA also was correlated with the severity of retinopathy present. Essential hypertension accounted for 57 (80 per cent) of the 71 cases. Among cases with higher grades of ITA, hypertension was of the essential variety in 20, and renal in origin in 14. This observation tended to confirm the contention (Connor *et al.*, 1957) that ITA is the only significant renal lesion that can be correlated with all types of renal hypertension. In the more severe grades of ITA, chronic glomerulonephritis and pyelonephritis (62 per cent) were often the basic lesions. Pyelonephritis was an almost constant finding in the presence of malignant hyper-

tension, which corroborates the belief (Saphir, 1952; 1959) that pyelonephritis is the underlying lesion in most cases of malignant hypertension. Of 18 cases of malignant hypertension in this study, 14 were associated with pyelonephritis and 2 with chronic glomerulonephritis, indicating that an ischemic mechanism may be the cause of this type of hypertension. In 6 of 8 patients from whom a kidney was removed for the relief of hypertension, ITA was present. The kidney removed was below normal weight, although renal function was good. In these patients, too, the degree of vascular sclerosis in the kidney was well correlated with the degree of tubular atrophy.

CLINICAL APPLICATION OF DIPHENYLTHIOCARBAZONE (DITHIZONE) IN CARCINOMA OF THE PROSTATE.

Lo, Mei-Chiau. *Canad. M. A. J.* **82:** 1203 (June 11) 1960.

The use of diphenylthiocarbazone in prostatic cancer was suggested by the experimental finding that the zinc-chelating agent suppressed prostatic function in dogs, that is, prostatic fluid volume, Zn^{65} uptake, zinc concentration, and the histologic appearance of the prostate gland. A preparation of the drug was made by suspending 160 mg. in 3 ml. of propylene glycol and adding 1 drop of 28 per cent ammonium hydroxide. This solution was diluted in 100 to 200 ml. of 5 per cent glucose in water before infusing it intravenously at a rate of 20 to 60 drops per minute. The dose varied between 10 and 20 mg. per Kg. Of the 10 patients treated, (*a*) 3 had prostatic cancer diagnosed for the first time and had had no hormonal treatment; (*b*) 4 had no evidence of metastases and were receiving estrogen therapy; this was discontinued and testosterone was given before and during treatment with diphenylthiocarbazone; and (*c*) 3 had advanced carcinoma of the prostate with metastases and had been treated by estrogen and orchiectomy. The most striking effect was relief of pain from bony metastases in all of the 3 cases with such pain. Dysuria, frequency, and nocturia were decreased in most cases. The appetite was improved or became normal. No loss in body weight occurred. After treatment, the prostate gland was usually softer and diminished in size. The infusion usually caused induration along the vein. A mild transient headache occurred during infusion in 2 patients but persisted for twelve hours in one of them. Other reactions were a diffuse rash in 2 patients and superficial thrombophlebitis in 4 patients. The serum bilirubin level was elevated in 6 patients, and bromsulphalein retention and the blood urea nitrogen level were elevated in 2 patients. A slight increase in alkaline phosphatase activity occurred twice; fluctuating levels were noted in 2 other instances. A transient decrease in hemoglobin concentration occurred in some instances. Other biochemical tests and urinalyses yielded no abnormal results. Histologic changes consisted of atrophy and degeneration of the neoplastic acini. The degree of these alterations varied from mild changes in the cells to gross shrinkage of neoplastic tissue in which reduced cytoplasmic volume, reduction of nuclear size, and pyknosis also were noted. Well preserved acini were interspersed among these changed acini. Two patients in the series died, one from renal failure. The surviving patients have been followed for seven months without evidence of recurrence.

BISACODYL (DULCOLAX): AN EVACUANT SUPPOSITORY. A CONTROLLED THERAPEUTIC TRIAL IN CHRONICALLY ILL AND GERIATRIC PATIENTS.

Mandel, L., and Silinsky, J. *Canad. M. A. J.* **83:** 384 (Aug. 20) 1960.

A controlled therapeutic trial to evaluate the efficacy of a new bowel evacuant, bisacodyl (Dulcolax), was carried out on a group of chronically ill and aged patients. The suppository only was investigated, and glycerine suppositories were used as the control preparation. Each patient acted as his own control. In addition, the administration of the control suppository and agent under trial to consecutive patients was conducted at random. Forty-one patients were included in the trial. Bisacodyl produced a superior result in 24; glycerine was more effective in 7; and in 10 patients the response to each was the same. Statistical

analysis of these results by the sign test showed that there was a statistically significant difference between the results for bisacodyl and for glycerine. It is concluded that suppositories of bisacodyl are superior to those of glycerine in the treatment of chronic constipation and dyschezia in chronically ill and aged patients. (From authors' summary and conclusions.)

SUCCESSFUL EXTERNAL ELECTRICAL DEFIBRILLATION IN ACUTE MYOCARDIAL INFARCTION. REPORT OF A CASE.

Nast, P. R.; Pennypacker, C. S., and Wagner, J. A. *Circulation* **22:** 138 (July) 1960.

Ventricular fibrillation may be the cause of "sudden death" in patients with acute myocardial infarction. Distinguishing this arrhythmia from cardiac standstill by means of the electrocardiogram and immediate treatment may result in successful resuscitation. External defibrillation appears to be more feasible than thoracotomy with cardiac massage, because of the age of the patients affected and because the method has not often resulted in survival. A case is reported of a patient with an acute myocardial infarction in whom ventricular fibrillation persisted for six minutes. Regular sinus rhythm was restored within two minutes after external defibrillation with the Zoll-Electrodyne External Defibrillator with the use of 60-cycle alternating current at 350 volts every ten seconds for three shocks. This is the only case of its kind. Defibrillation in other patients with acute myocardial infarction and ventricular fibrillation has resulted in either ventricular standstill not responsive to external cardiac pacemakers or recurrent ventricular fibrillation and death.

SUBDURAL HEMATOMA COMPLICATING ANTICOAGULANT THERAPY.

Pan, A.; Rogers, A. G., and Pearlman, D. *Canad. M. A. J.* **82:** 1162 (June 4) 1960.

The bilateral subdural hematomas in the male patient reported, were evacuated; he did well postoperatively until the occurrence of a second myocardial infarction that proved fatal. This is a rare complication of anticoagulant therapy, 6 cases of hematoma having previously been reported with only 1 patient surviving. In each of these patients, the prothrombin time was prolonged beyond the margin of safety. This emphasizes the necessity of careful supervision of anticoagulant therapy with frequent adjustment of dosage according to determinations of prothrombin time. The literature with regard to contraindications to anticoagulants and hemorrhagic complications resulting from their use is reviewed, with emphasis on central nervous system involvement. Thus hemorrhage may occur in the central nervous system during anticoagulant therapy, particularly in patients with hypertension with previous cerebrovascular accidents. These may be intracerebral, intracerebellar, intraventricular, subarachnoid, subdural, or intraspinal, or extradural hemorrhage of the spinal cord, or hemorrhage in the mid-brain, pons, or medulla oblongata.

CIRCULATORY EFFECTS OF GUANETHIDINE. CLINICAL, RENAL, AND CARDIAC RESPONSES TO TREATMENT WITH A NOVEL ANTIHYPERTENSIVE DRUG.

Richardson, D. W.; Wyso, E. M.; Magee, J. H., and Cavell, G. C. *Circulation* **22:** 184 (Aug.) 1960.

Guanethidine (Ismelin), a new synthetic antihypertensive drug, is believed to interfere with the release of norepinephrine from sympathetic nerve endings. It does not inhibit parasympathetic activity. This drug was given for periods up to six months to 25 men with severe hypertension, intravenously in a dose of 150 to 200 mg. the first day, half of this amount the second day, and 25 to 75 mg. daily thereafter. The maintenance dosage was determined as the amount to produce maximum reduction in blood pressure without disturbing side-effects. Blood pressure was appreciably reduced in every man, the diastolic

pressure falling an average of 23 mm. Hg with the patient supine and 45 mm. Hg standing. The response was maximum in forty-eight to seventy-two hours. The blood pressure remained at the lowest levels for several days after the drug was stopped. Orthostatic dizziness and fainting, which occurred in 15 patients, could be relieved by placing the patient in the supine position. Mild diarrhea was the only other common side-effect. Failure of ejaculation occurred in 2 patients. No parasympatholytic effects were observed. Satisfactory reduction in blood pressure could be achieved with average maintenance dosages of 50 mg. daily in 9 of 11 patients followed for two to six months after discharge from the hospital. Orthostatic dizziness in 2 of these patients prevented adequate control of blood pressure. It was found that guanethidine reduced cardiac output, and apparently lowered blood pressure by this means rather than by relaxing arteriolar constriction, since peripheral resistance decreased only slightly. The reduction in cardiac output was accompanied by a decrease in heart rate, so that the volume of blood pumped per beat remained relatively constant—a finding that suggested that guanethidine inhibits sympathetic cardio-accelerator stimuli. The glomerular filtration rate and renal blood flow were reduced during administration of the drug. The blood urea nitrogen level rose moderately during treatment in patients in whom it exceeded 25 mg. per 100 ml. in the control period. In no case did progressive azotemia or oliguria cause cessation of therapy. Renal function returned to pretreatment levels when the drug was discontinued.

THE EFFECT OF PYRIDOXINE ANTAGONISTS IN THE CARCINOID SYNDROME.
Schrodt, G. R.; Dizon, F. Y.; Peskoe, L. Y.; Howell, R. S.; Robie, C. H., and Stevenson, T. D. *Am. Pract. & Digest Treat.* **11:** 750 (Sept.) 1960.

Experimental studies have showed that serotonin production is diminished in pyridoxine-deficient animals. Therefore, pyridoxine antagonists were tried in 2 patients with the carcinoid syndrome. The diagnosis was confirmed by finding large amounts of 5-hydroxyindole acetic acid in the urine. Treatment with 100 mg. of desoxypyridoxine per day produced pyridoxine deficiency in one of the patients; in the second patient, the dosage necessary was 200 mg. in combination with isonicotinic acid hydrazide. However, no change occurred in the symptoms of either patient. In the first patient, scarcely any decrease in 5-HIAA in the urine occurred; in the second patient, the excretion was lowest after INH had been added. At necropsy, both patients were found to have mitral as well as pulmonic and tricuspid valve involvement. The origin of the endocardial thickening and valvular changes in the carcinoid syndrome is not known. It is pointed out that the patient with carcinoid syndrome may have niacin, tryptophane, and protein deficiencies. These may not account for the endocardial changes but may be conditioning factors. The presence of a nutritional deficiency in the carcinoid syndrome is emphasized by a low serum vitamin B_{12} level in one of the patients in this series.

EFFECT OF AGE ON PULSE WAVE VELOCITY AND "AORTIC EJECTION TIME" IN HEALTHY MEN AND IN MEN WITH CORONARY ARTERY DISEASE.
Simonson, E., and Nakagawa, K. *Circulation* **22:** 126 (July) 1960.

Impedance plethysomograms were taken in 51 healthy men and 42 normotensive men with coronary heart disease, from the aorta near the place of auscultation of the aortic valve and from the femoral artery in the femoral triangle, recorded simultaneously with the three electrocardiographic standard leads. The aortic pulse wave velocity was determined from the time interval between the foot points of the aortic and femoral volume pulse, and the anatomic distance between the electrodes. It increases with age in normal subjects as well as in patients, but the values are significantly higher in the patients. These results are suggestive of accelerated degenerative changes in the aorta, probably due to atherosclerosis. The interval from the earliest detectable QRS deflection to the foot point of the aortic volume pulse ("aortic ejection time") becomes longer with age in the normal group.

In patients with coronary artery disease, the prolongation is significantly larger for each of three age subgroups. The results suggest that ventricular ischemia affects ventricular isometric contraction. (From authors' summary.)

CARBOHYDRATE METABOLISM IN ATHEROSCLEROSIS.
Waddell, W. R., and Field, R. A. *Metabolism* **9:** 800 (Sept.) 1960.

In 47 patients with atherosclerosis, carbohydrate metabolism was studied by glucose tolerance, insulin tolerance, and glucagon tests. Changes in nonesterified fatty acids (NEFA) were followed in 10 of these patients during these tests. The tests demonstrated that this group of patients had a relative unresponsiveness to hyperglycemia and hypoglycemia, despite a normal fasting blood sugar level, and an impaired response of adipose tissue to glucose loads, as evidenced by a failure of the serum NEFA level to fall in response to the hyperglycemia induced by glucagon. These findings are consistent with the definition of mild, stable diabetes, and one quarter of the patients had a family history of diabetes. The observed abnormal carbohydrate metabolism may have no direct relation to atherosclerosis; however, clinical observations on the development of vascular disease in diabetic patients, the known interrelationships between normal carbohydrate and lipid metabolism, and the abnormal lipid metabolism in diabetes suggest an etiologic connection between carbohydrate metabolism and atherosclerosis. (From authors' summary.)

GERIATRIC PSYCHIATRIC PATIENTS IN GENERAL HOSPITAL AND MENTAL HOSPITAL.
Ward, T. F., and Ross, H. F. *Canad. M. A. J.* **82:** 1151 (June 4) 1960.

Two groups of geriatric psychiatric patients, one admitted to a general hospital psychiatric unit and one to a mental hospital during one year, are compared. A survey was made of such general characteristics as age, sex, and length of stay. The patients were grouped in 5 clinical categories: affective, psychoneurotic, organic, schizophrenic, and senility and physical disease. The results of treatment were determined at the time of discharge and one and a half years after discharge. When data for the entire group (101 males and 90 females) were compared with those for Canada as a whole, the former contained a disproportionately large number of persons senile and physically ill. Divided by treatment facility, the majority of these were in the mental hospital group. A significantly greater number of male patients with affective diseases were admitted to the general hospital, whereas a larger proportion of male patients with organic disease were admitted to the mental hospital. Ninety-eight per cent of patients could be discharged from the psychiatric unit but only 45 per cent from the mental hospital. Death rates were greater for males than for females, and this was accounted for particularly by the greater number of deaths among males admitted to a mental hospital. At follow-up, it appeared that males admitted to the psychiatric unit were better able to stay out of the hospital after they had been discharged. This study points up the problem of separating the predominantly psychiatric patients from those physically ill. The latter belong in institutions for the treatment of medical diseases and do poorly in mental hospitals. One of the difficulties of separating these patients is the lack of a proper definition for the psychiatric syndromes that appear. It is a fallacy to consider an elderly person with obvious mental symptoms as psychotic, since there are many nonorganic conditions that respond well to treatment and have a good prognosis. Among patients who improve in the hospital, females have a better over-all ability to survive and have a good prognosis. A remarkable aspect of the study was the low number of previous admissions; the geriatric group seemed to have been able to postpone their emotional difficulties until the physical and mental stresses of old age had caused them to become ill. Another important finding of this study was the high number of initial mental patients who remained in the hospital at the time of follow-up, and in poor mental health. Patients in poor physical condition will have died, but those in good condition with a mental illness will present a problem in care for the rest of their lives. The question is raised as to whether a separate institution is needed for them.

UN CAS DE LEUCÉMIE LYMPHATIQUE SUBAIGUË AVEC DES MANIFESTATIONS CAVITAIRES PROPREMENT LEUCÉMIQUES AUX POUMONS (A CASE OF SUBACUTE LYMPHATIC LEUKEMIA WITH CAVITARY MANIFESTATIONS IN THE LUNG).

Yigitbasi, O., and Mamaoglu, K. *Presse méd.* **68** (21): 823–824, 1960; through Ciba Literature Review **5:** 207, 1960.

The rare occurrence of a cavity in the lung caused by leukemia recently was observed in Turkey. The possibility that the pulmonary lesion was due to tuberculosis or some other condition could be excluded. The patient, a 60-year-old woman, complained initially of dyspnea on effort and later of dyspnea at rest. She had a cough accompanied by a small amount of whitish sputum that was not malodorous. Clinical, hematologic, and myelographic findings led to a diagnosis of subacute lymphatic leukemia. A week after hospital admission, expectoration increased and blood appeared in the sputum. A roentgenogram showed a pulmonary infiltrate which developed into a cavity. Treatment was initiated with 30 mg. of prednisolone daily, whereupon the leukocyte count fell to 22,400 within five days, and later to 12,000 to 14,000. The quantity of sputum declined from about 100 to 40 ml. The patient was discharged after seven weeks and was followed as an outpatient. Prednisolone gradually was reduced to 10 mg. daily. The cough and expectoration decreased steadily and eventually subsided completely. The patient's general condition and appetite were satisfactory, and the cavity closed. The last examination showed one lymph node the size of a walnut, and another the size of a hazelnut.